22 April 2022
EMA/622447/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yescarta

International non-proprietary name: axicabtagene ciloleucel

Procedure No. EMEA/H/C/004480/II/0042

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
Allo-SCT	allogeneic SCT
ADR	adverse drug reaction
AUC_{0-28}	area-under-the-curve from Day 0 to Day 28
Auto-SCT	autologous stem cell transplant
CAR	chimeric antigen receptor
CI	confidence interval
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL 10	C-X-C motif chemokine 10
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EU	European Union
EZH2	enhancer of zeste homolog 2
FAS	full analysis set
FL	follicular lymphoma
FLIPI	follicular lymphoma international prognostic index
GM-CSF	granulocyte-macrophage colony-stimulation factor
GVHD	graft-versus-host disease
IAS	inferential analysis set
iNHL	indolent non-Hodgkin lymphoma
ICAM	Intercellular adhesion molecule
IFN-γ	Interferon-gamma
IL	Interleukin
IWG	International Working Group
KM	Kaplan-Meier
LLOQ	lower limit of quantification
MAA	market authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone
R-CVP	rituximab plus cyclophosphamide, vincristine and prednisone

PR	partial response
r/r	relapsed/refractory
RCR	replication-competent retrovirus
SAE	serious adverse event
SMR	standardized mortality ratio
SOC	system organ class
TNF-alpha	tumor necrosis factor alpha
TTNT	time to next therapy
US	United States
VCAM-1	Vascular cell adhesion molecule-1
VIS	vector integration sites

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Kite Pharma EU B.V. submitted to the European Medicines Agency on 23 July 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC and Package Leaflet are proposed to be updated. As a consequence, the RMP (version 5.1) has been updated to align with the indication extension.
In addition, the applicant has taken the opportunity to make minor editorial corrections throughout the SmPC and package leaflet to align with the current Quality Review of Documents (QRD) template.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Yescarta was designated as an orphan medicinal product EU/3/15/1579 on 11 November 2015 in the following indication: Treatment of follicular lymphoma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0132/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0132/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Claire Beuneu

Timetable	Actual dates
Submission date	23 July 2021
Start of procedure:	14 August 2021
CAT Rapporteur Assessment Report	11 October 2021
CAT Co-Rapporteur Assessment Report	20 October 2021
PRAC Rapporteur Assessment Report	15 October 2021
PRAC members comments	20 October 2021
CAT and CHMP members comments	26 October 2021
PRAC Outcome	28 October 2021
Updated CAT Rapporteur(s) (Joint) Assessment Report	29 October 2021
CAT Request for Supplementary Information (RSI)	5 November 2021
CAT Rapporteur Assessment Report	25 January 2022
PRAC Rapporteur Assessment Report	27 January 2022
PRAC members comments	01 February 2022
CAT and CHMP members comments	08 February 2022
PRAC Outcome	10 February 2022
Updated CAT Rapporteur Assessment Report	14 February 2022
CAT Request for Supplementary Information (RSI)	17 February 2022
CAT Rapporteur Assessment Report	4 April 2022
CAT and CHMP members comments	6 April 2022
Updated CAT Rapporteur Assessment Report	14 February 2022
CAT Opinion	13 April 2022
CHMP Opinion	22 April 2022
The CAT adopted a report on similarity of Yescarta with Gazyvaro and Kymriah (Appendix 1)	13 April 2022
The CAT adopted a report on the significant clinical benefit for Yescarta in comparison with existing therapies (Appendix 2)	13 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) with increasing occurrence (1/100.000; ESMO 2020). The median age of diagnosis is approx. 60 years of age; however, occurrence in younger age is possible (*J Clin Exp Hematop, Vol 54,June 2014)*. FL develops due to proliferation of neoplastic germinal center B cells, both centrocytes (small to medium sized cleaved cells) and centroblasts (large non-cleaved cells) that have a follicular pattern of growth (*Kahl 2016*). FL is subject of various classifications according to the proportion of centroblastic cells, molecular genetics, immunhistochemics and clinical appearance. The current WHO edition defines FL in accordance to number of centroblastic cells as Grade 1, Grade 2, Grade 3A and Grade 3B. The distinction between Grade 3A and 3B is important due to their apparent differences in molecular genetics and prognosis; it is suggested that Grade 3A FL (no centrocytes, centroblasts only) is on the same spectrum as Grade 1-2 FL, and Grade 3B FL behaves as de novo DLBCL (*Katzenberger et al., Am J Pathol 2004; Karube et al., Blood 2007).* Clinical classification and score grading are the Ann Arbor classification, which specifies stage I-IV based on lymph node regions and class A (without symptoms) and B (with symptoms), and the Follicular Lymphoma International Prognostic Index (FLIPI from the pre-rituximab era and FLIPI2 for rituximab-treated patients), which is used for the stratification of patients into low-, intermediate-, or high-risk groups. The clinicogenetic risk score m7-FLIPI, published 2015 in Lancet Oncology by Pastore A et al., is based on FLIPI score and mutation status of seven candidate genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP* and *CARD11).* Based on an observation of clinical characteristics of 95 patients with FL, *Lockmer et al., BJHaem 2019* concluded, however that the prognostic factor may be different when applied in a context of different therapeutically agents.

Treatment

The heterogeneity of FL in terms of clinical, histological and molecular-genetic presentation both at initial diagnosis and increasingly in the course of the disease, which is highly variable both between patients and intra-patient (*Kahl&Yang, 2016; Fredman, 2018; Lockmer at al.*) due to the risk of histological transformations, explains the challenges, clinicians are facing. Although there are numerous therapeutically options, there seems to be a lack of robust tools for initiation of the right treatment regimen to the right time.

Newly diagnosed, low-grade, limited stage FL is often responsive to first-line treatments. Advanced stage FL generally requires multiple successive lines of therapy leading to shorter remission periods, chemo-refractory disease and transformation to diffuse large B-cell lymphoma (DLBCL) (about 40% of all FL patients). Transformed follicular lymphomas (tFL) have a worse prognosis due to poorer response to treatment than primary DLBCL. Surgery is not used as a general treatment option; however, removing of symptomatic limited affected organs/tissue may be useful in some cases.

For patients with limited low tumor burden stages I-II, a radiotherapy-based treatment with or without combination with rituximab is clinical standard followed by consolidation/maintenance, e. g. with rituximab for 2 years. Myeloablative consolidation followed by ASCT prolongs PFS, but advantage on OS has not been

observed (*Schaaf et al, Cochrane Database Syst Rev 2012).* Patients in advanced stages of FL or cases where radiotherapy is not feasible are treated with systemic (combined) chemo-immunotherapy, immunomodulatory agents and phosphatidylinositol 3-kinase (PI3K) inhibitors. Complete response (CR) rates are low, however, ranging from 1% to 14% (*Dreyling 2017)*. Autologous (auto-SCT) and allogeneic stem cell transplant (allo-SCT) may benefit only a small fraction of patients. Therefore, most of the patients will experience disease progression, relapse or refractory disease, and prognoses for these patients are poor. Despite the advances in the treatment of FL, there is an unmet need for patients with refractory and/or relapsed FL, who failed on available therapies.

Figure 1. ESMO Recommendations for low tumour burden FL (November 2020)

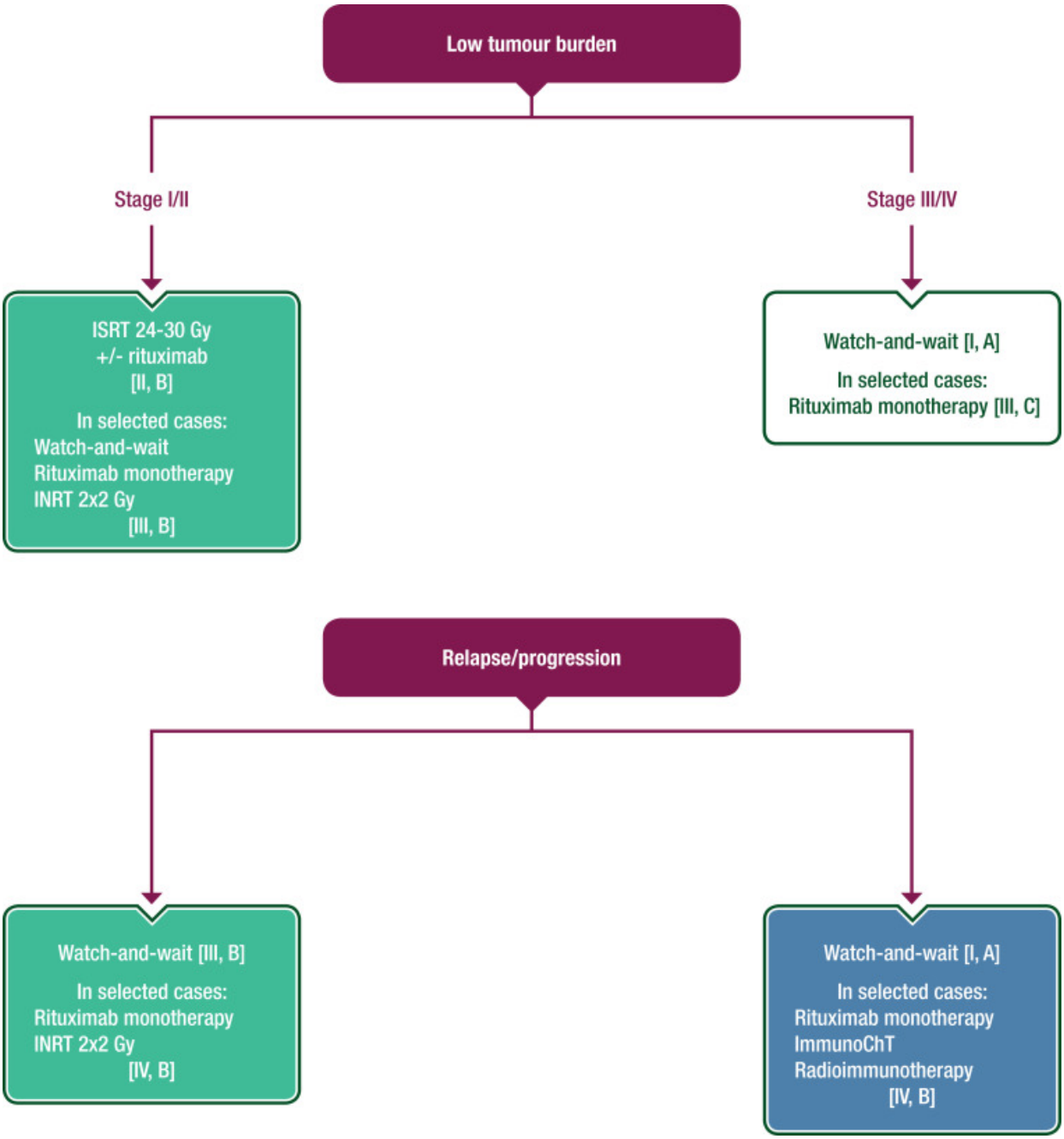
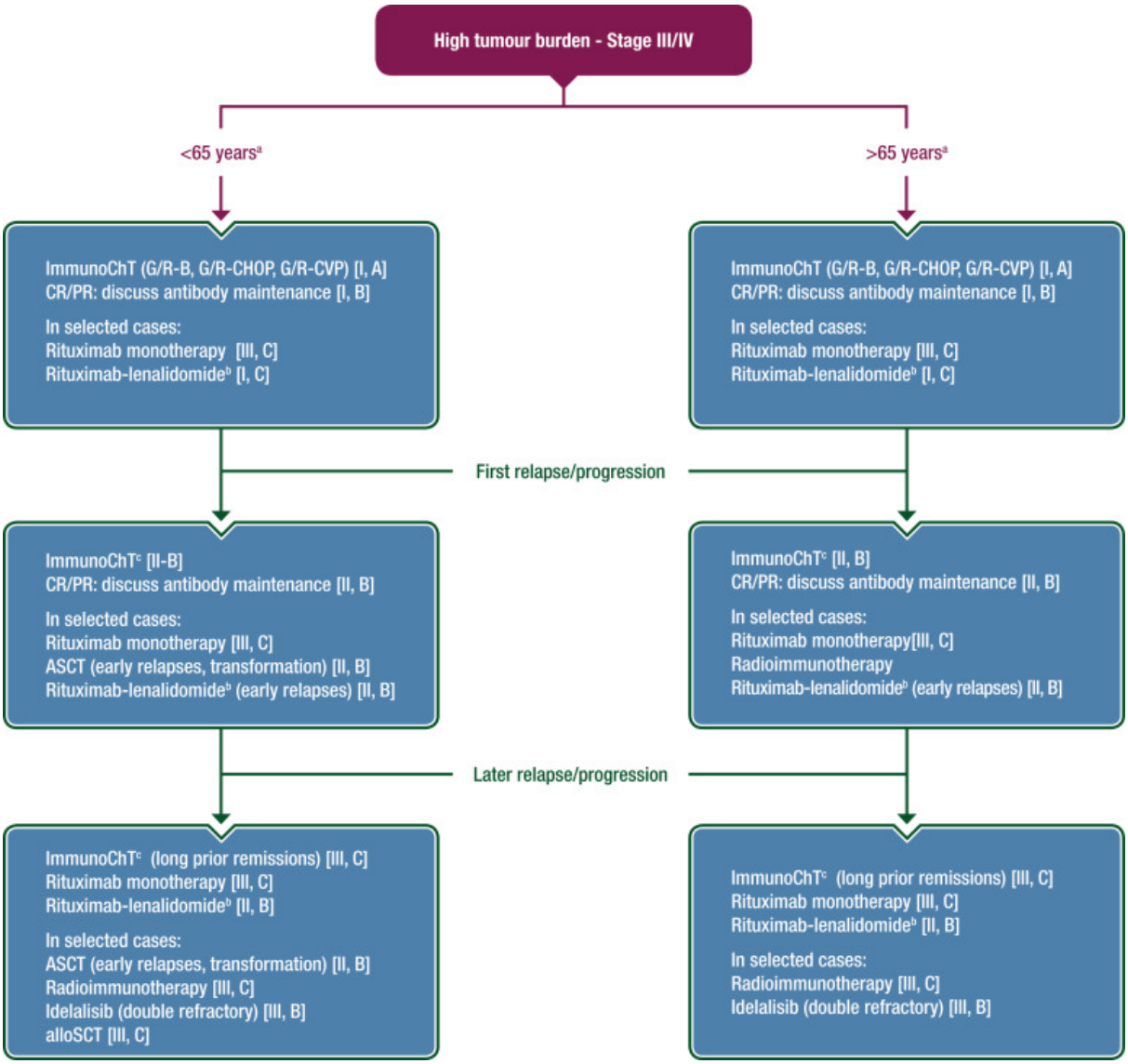


Figure 2. ESMO Recommendations for high tumour burden FL (November 2020)



Claimed therapeutic indication

The claimed indication is: "Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy".

Aetiology and pathogenesis

FL is a systemic neoplasm of the lymphoid tissue displaying germinal centre (GC) B cell differentiation. The tumorigenesis starts in precursor B cells and becomes full tumour when the cells reach the GC maturation step. FL is preceded by an asymptomatic preclinical phase in which premalignant B cells carrying a t(14;18) reciprocal chromosomal translocation develop additional genetic alterations, although not all of these cells progress to the tumour phase. The aetiology of FL is unknown; family history is important (*Br J Haematol 2009*) and t(14;18) alone is considered not sufficient to cause FL (*Haematologica, 2014*).

2.1.2. About the product

Axicabtagene ciloleucel is an autologous CAR T-cell product in which a subject's T cells are engineered to express receptors consisting of a single-chain antibody fragment against CD19 linked to CD3ζ and CD28 T-cell activating domains that result in elimination of CD19-expressing cells {Jackson 2016, Roberts 2018}. Following CAR engagement with CD19+ target cells, the CD3ζ domain activates the downstream signaling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity {Roberts 2018}. The intracellular signaling domain of CD28 provides a costimulatory signal that works in concert with the primary CD3ζ signal to augment T-cell function, including interleukin (IL)-2 production {Finney 1998}. Together, these signals stimulate proliferation of the CAR T cells and direct killing of target cells. In addition, activated T cells secrete cytokines, chemokines, and other molecules that can recruit and activate additional antitumor immune cells {Restifo 2012}.

Yescarta was approved in 2018 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy. A single dose of Yescarta contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

2.1.3. General comments on compliance with GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Quality aspects

No changes are proposed for the manufacturing of the medicinal product, which is therefore considered to be the same, including all DS and DP specifications.

2.3. Non-clinical aspects

One additional non-clinical genotoxicity study has been submitted in the application. The genotoxic potential of axicabtagene ciloleucel is related to the risk of insertional oncogenesis as a result of vector integration into the genome of T cells. The risk of insertional oncogenesis is not affected by the proposed extension of indication.

The risk of insertional oncogenesis has previously been assessed by literature review and the clinical experience gained with administration of human T cells that were transduced with γ-retroviral vectors. The newly submitted non-clinical genotoxicity study investigated the vector integration sites (VIS) in anti-CD19 CAR T cells generated using the KTE-C19 manufacturing process and T cells from three healthy donors. The data revealed an even VIS diversity for all three donors at the end of manufacturing. No over-represented VIS could be detected suggesting that no transduced T-cell clone had acquired a significant growth advantage resulting from the integration event.

2.3.1. Ecotoxicity/environmental risk assessment

The environmental risk of axicabtagene ciloleucel is not affected by the proposed extension of indication.

2.3.2. Conclusion on the non-clinical aspects

The additional non-clinical data do not raise any concerns and complement the literature review and clinical experience gained so far.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol Number	Study Title	Third Country
KTE-C19-105 (ZUMA-5)	A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL) Ongoing	United States
KTE-C19-101 (ZUMA-1)	A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma Ongoing	Canada, Israel, United States
KTE-C19-109 (ZUMA-9)	A Multicenter, Open-label, Expanded Access Study of Axicabtagene Ciloleucel for the Treatment of Subjects with Relapsed/Refractory Large B-cell Lymphoma Ongoing Cohort 2 is enrolling subjects whose commercially manufacture products do not meet commercial release specifications	Canada, United States
KTE-C19-112 (ZUMA-12)	A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Subjects with High-Risk Large B-Cell Lymphoma Ongoing	Australia, Canada, United Kingdom, United States

2.4.2. Pharmacokinetics

General

Methods, endpoints and objectives for primary/secondary Analysis on PK/PD

The pharmacokinetic and pharmacodynamic data for axicabtagene ciloleucel in this application are based on 1 clinical study: KTE-C19-105 (ZUMA-5). ZUMA-5 is a Phase 2, multicenter, ongoing open-label study evaluating the efficacy of axicabtagene ciloleucel in subjects with r/r B-cell iNHL of FL or MZL histological subtypes. Evaluations of pharmacokinetics (PK) and pharmacodynamics (PD) of axicabtagene ciloleucel were included as secondary endpoints. The results on PD are provided in the primary analysis report with the data cutoff date of 12 March 2020 only, and PK-parameters are evaluated and provided both in the primary analysis report with the data cutoff date of 12 March 2020 and in the 18-months analysis addendum with DCO 14 September 2020. The assessments were based on known or hypothesized aspects of the axicabtagene ciloleucel mechanism of action, and the current knowledge of the safety profile of the lymphodepleting chemotherapy regimen and of axicabtagene ciloleucel infusion. The number, frequency, and timing of blood or serum samples collected for PK and PD analyses were based on the expected concentration-time profile of axicabtagene ciloleucel. Presented subgroup analyses should be considered descriptive only, as the study was not designed to test for differences between groups.

The safety analysis set was used for summary analyses of PK and PD and correlation to safety outcomes. At the cut-off date of 12 March 2020 and 14 September 2020, the safety analysis set comprised respectively 146 and 148 subjects with iNHL treated with any dose of axicabtagene ciloleucel, including 124 subjects with FL and 22 (24 for 18-month update) subjects with MZL.

The inferential analysis set was used for correlation to clinical efficacy outcomes. The inferential analysis set comprised 104 subjects, including 84 subjects with FL and 20 subjects with MZL.

Assessments at the time of the primary analysis (data cut-off date of 12 March 2020) included presence, expansion, and persistence of gene-marked anti-CD19 CAR T cells in blood (PK parameters), levels of B cells in blood over time (to monitor on-target/off-tumor effect), and levels of key soluble analytes (cytokines and chemokines) in serum over time (PD parameters). Exploratory correlative analyses of PK and PD results with baseline characteristics and clinical outcomes were also performed.

The presence, expansion, and persistence of anti-CD19 chimeric antigen receptor (CAR) T cells were measured in cryopreserved peripheral blood mononuclear cells (PBMCs) derived from whole blood of subjects treated in ZUMA-5. Serial blood samples were taken after cell infusion and subjected to a validated quantitative polymerase chain reaction (qPCR) assay. The qPCR assay was based on the method developed by Kochenderfer and colleagues {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a} and was further optimized and validated by the University of Rochester Medical Center (URMC) Central Lab Services. The qPCR assay was demonstrated to be specific for cells with a stably integrated anti-CD19 CAR transgene. The lower limit of detection was established at 1 cell equivalent per 100,000 PBMCs (0.001%), and the lower limit of quantification (LLOQ) was established at 8 to 110 cell equivalents per 100,000 PBMCs depending on DNA sample load.

Table 1: Pharmacological Methods Used in ZUMA-5

Category/Method	Description

Pharmacokinetics	
Sampling times	• At enrollment/leukapheresis (prior to lymphodepleting chemotherapy), after infusion on Day 7, Week 2, Week 4, Month 3, Month 6, then every 6 months through Month 24 and annually thereafter • On the day of unscheduled hospital re-admission with any axicabtagene ciloleucel-related AE, then weekly during hospitalization, and on the day of discharge • At the time of disease progression
Assay for anti-CD19 CAR T cells in PBMCs	Validated qPCR method adapted from NCI method {Kochenderfer 2012, Kochenderfer 2015, Kochenderfer 2017a}, see m5.3.1.4
Pharmacodynamics	
Serum sampling times	• At enrollment/leukapheresis (prior to lymphodepleting chemotherapy), Day 0, and after infusion on Day 3, Day 7, Week 2, and Week 4 • At the time of Grade 3 axicabtagene ciloleucel-related toxicity • On the day of unscheduled hospital re-admission with any axicabtagene ciloleucel-related AE, then weekly during hospitalization (every other day during hospitalization for a new or ongoing Grade 3 or higher neurological event), and on the day of discharge
Methods (see m5.3.1.4)	
MSD® V-PLEX® Plus panels (Rockville, MD)	IL-7, IL-15 (BED-02454, REP-00255) CRP, ICAM-1, VCAM-1 (BED-01484, REP-00256) TNF-α, IL-2, IL-10, IL-6, IFN-γ, IL-8 (BED-02361, REP-00257) CXCL10 (BED-01482, REP-00258)
Simple Plex™ ELISA (ProteinSimple®; San Jose, CA)	IL-1RA (SOP-00572, REP-00380) IL-2Rα (BED-02157, REP-17900) Ferritin (SOP-00476)
MILLIPLEX® MAP human $CD8^+$ T-cell panel (EMD Millipore®)	Granzyme B, perforin (SOP-00332)

Table 2: Pharmacologic Objectives and Endpoints for ZUMA-5

Category	Description
Phase	2
Study design	Open-label efficacy; multicenter
Study population	Adult subjects with relapsed or refractory B-cell indolent non-Hodgkin lymphoma of FL or MZL histological subtypes

Analysis population for pharmacokinetics and pharmacodynamics[a]	Safety analysis set (all subjects treated with any dose of axicabtagene ciloleucel):
	• iNHL: N = 146
	  FL: N = 124
	  MZL: N = 22
	Inferential analysis set (all subjects enrolled [and who met the eligibility criteria for the pivotal cohort, ie, had 2 or more prior therapies] and treated with any dose of axicabtagene ciloleucel):
	• iNHL: N = 104
	  FL: N = 84
	  MZL: N = 20

Study pharmacokinetic and pharmacodynamic objectives	Secondary: • To assess levels of anti-CD19 CAR T cells in blood and levels of cytokines in serum and association with clinical outcomes
Study pharmacokinetic and pharmacodynamic endpoints	Secondary: • Levels of anti-CD19 CAR T cells in blood • Levels of cytokines in serum
Lymphodepleting chemotherapy regimen	Cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 given concurrently for 3 consecutive days (Days −5, −4, and −3 relative to the axicabtagene ciloleucel infusion on Day 0)
Axicabtagene ciloleucel dose, route, regimen	Target dose of 2 x 10^6 anti-CD19 CAR T cells/kg body weight[b] in a single intravenous infusion on Day 0
Duration of follow-up	Up to 15 years

a Sample sizes are based on a data cutoff date of 12 March 2020 for primary analysis.

b Among subjects with FL, the median weight-adjusted dose of axicabtagene ciloleucel was 2.0 x 10^6 anti-CD19 CAR T cells/kg (range: 1.3 x 10^6 to 2.1 x 10^6 cells/kg). Among subjects with MZL, the median weight-adjusted dose of axicabtagene ciloleucel was 2.0 x 10^6 anti-CD19 CAR T cells/kg (range: 1.6 x 10^6 to 2.0 x 10^6 cells/kg)

Results on Pharmacokinetics

Pharmacokinetic results over time are shown in Table 3. Of the 114 subjects evaluable at Month 3, 15 (12.10%) had anti-CD19 CAR T-cell levels below the LLOQ, ie, no cells detected. Anti-CD19 CAR T cells remain detectable at Month 6 in the majority of subjects with evaluable samples at the time of the data cutoff date (83 of 106 subjects, 66.94%). Anti-CD19 CAR T cells remain detectable at Month 12 in 65 of 85 subjects (52.42%) with evaluable samples at the time of the data cutoff date. Anti-CD19 CAR T cells remain detectable at Month 18 in 26 of 36 subjects (20.92%) with evaluable samples at the time of the data cutoff date. At Month 24, anti-CD19 CAR T cells were detectable in 18 of 25 subjects (14.52%) with evaluable samples at the time of the data cutoff date (14 Sep 2020).

Table 3: Pharmacokinetic Results Over Time (Safety Analysis Set)

	Follicular Lymphoma (N = 124)	**Marginal Zone Lymphoma (N = 24)**	**Overall (N = 148)**
AUC_{0-28} (cells/µL*days)			
n	124	24	148
Mean (STDEV)	1248.58 (2404.84)	1509.51 (1735.23)	1290.89 (2306.40)
Median (Q1, Q3)	422.48 (142.92, 1192.55)	630.31 (327.37, 2754.02)	454.77 (150.32, 1323.90)
Min, Max	5.93, 1.99E+04	23.75, 6468.17	5.93, 1.99E+04
Peak (cells/µL)			
n	124	24	148
Mean (STDEV)	121.30 (219.29)	139.10 (158.14)	124.19 (210.22)
Median (Q1, Q3)	37.6 (12.02, 125.07)	52.56 (24.26, 299.14)	39.38 (13.97, 127.32)
Min, Max	0.49, 1415.40	1.76, 453.09	0.49, 1415.40

Time To Peak (Days)

n	124	24	148
Mean (STDEV)	15.90 (36.81)	13.46 (4.85)	15.50 (33.74)
Median (Q1, Q3)	8 (8, 15)	15 (8, 16)	9 (8, 15)
Min, Max	8, 371	8, 29	8, 371

Baseline

n	124	24	148
Mean (STDEV)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Median (Q1, Q3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Min, Max	0.00, 0.00	0.00, 0.00	0.00, 0.00

Day 7

n	124	24	148
Mean (STDEV)	101.52 (220.03)	69.50 (127.86)	96.32 (207.87)
Median (Q1, Q3)	17.41 (3.20, 71.94)	13.87 (2.49, 48.13)	17.12 (3.15, 66.84)
Min, Max	0.01, 1415.40	0.53, 422.35	0.01, 1415.40

Week 2

n	112	22	134
Mean (STDEV)	41.62 (64.45)	98.64 (136.19)	50.99 (82.73)
Median (Q1, Q3)	14.14 (4.54, 52.26)	39.38 (20.70, 97.02)	20.17 (5.22, 56.97)
Min, Max	0.00, 322.58	0.31, 453.09	0.00, 453.09

Week 4

n	117	22	139
Mean (STDEV)	7.79 (20.27)	15.22 (25.51)	8.97 (21.26)
Median (Q1, Q3)	1.49 (0.35, 4.21)	4.64 (1.62, 15.72)	1.90 (0.41, 6.05)
Min, Max	0.00, 140.22	0.09, 103.94	0.00, 140.22

Month 3

n	114	20	134
Mean (STDEV)	0.78 (1.91)	0.59 (0.53)	0.75 (1.78)
Median (Q1, Q3)	0.34 (0.05, 0.72)	0.57 (0.06, 0.98)	0.36 (0.05, 0.76)
Min, Max	0.00, 15.75	0.00, 1.81	0.00, 15.75

Month 6

n	106	16	122
Mean (STDEV)	3.49 (28.89)	0.75 (2.29)	3.13 (26.94)
Median (Q1, Q3)	0.24 (0.01, 0.62)	0.15 (0.00, 0.34)	0.24 (0.01, 0.59)

Min, Max	0.00, 297.21	0.00, 9.29	0.00, 297.21

Month 12

n	85	8	93
Mean (STDEV)	1.19 (7.30)	0.16 (0.27)	1.10 (6.98)
Median (Q1, Q3)	0.13 (4.63E-03, 0.39)	0.03 (0.00, 0.26)	0.13 (4.31E-03, 0.39)
Min, Max	0.00, 67.27	0.00, 0.72	0.00, 67.27

Month 18

n	35	2	37
Mean (STDEV)	0.74 (2.04)	0.01 (0.02)	0.70 (1.99)
Median (Q1, Q3)	0.09 (0.00, 0.70)	0.01 (0.00, 0.03)	0.03 (0.00, 0.63)
Min, Max	0.00, 11.94	0.00, 0.03	0.00, 11.94

Month 24

n	25	0	25
Mean (STDEV)	0.67 (1.24)		0.67 (1.24)
Median (Q1, Q3)	0.14 (0.00, 0.65)		0.14 (0.00, 0.65)
Min, Max	0.00, 5.71		0.00, 5.71

Data cutoff date = 14Sep2020

Figure 3. Median Line Plot of Number of Anti-CD19 CAR T Cells in Blood by Disease Type (Safety Analysis Set)

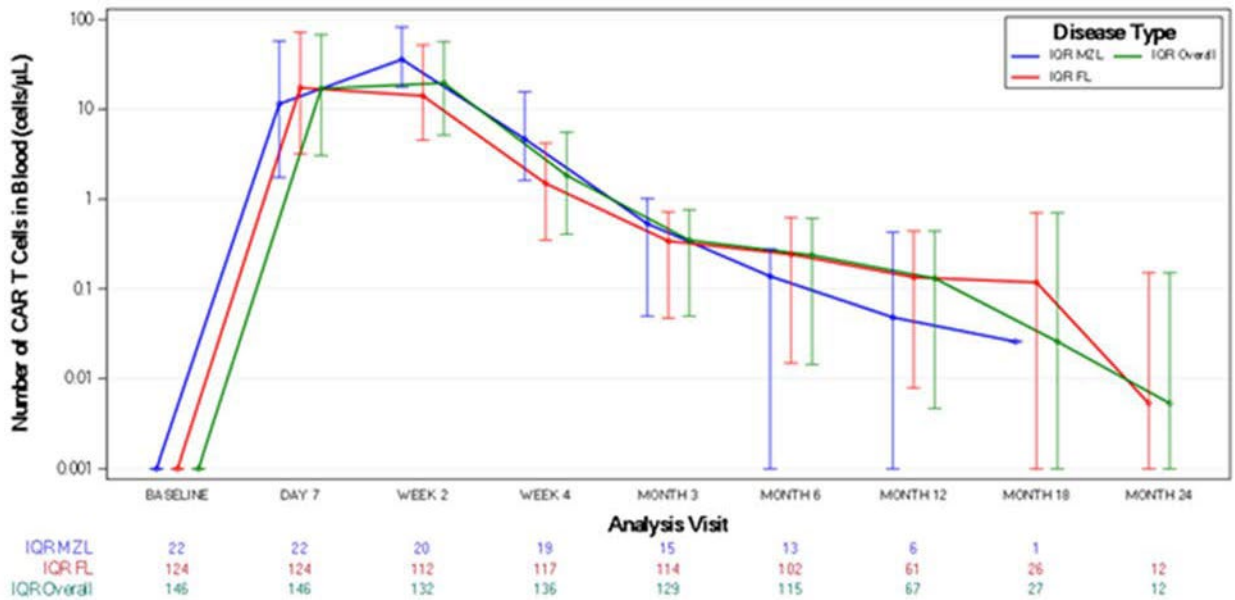
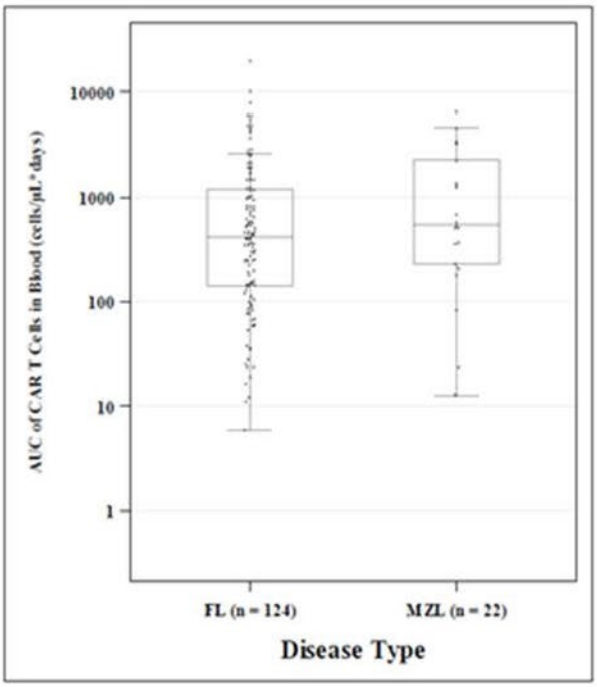
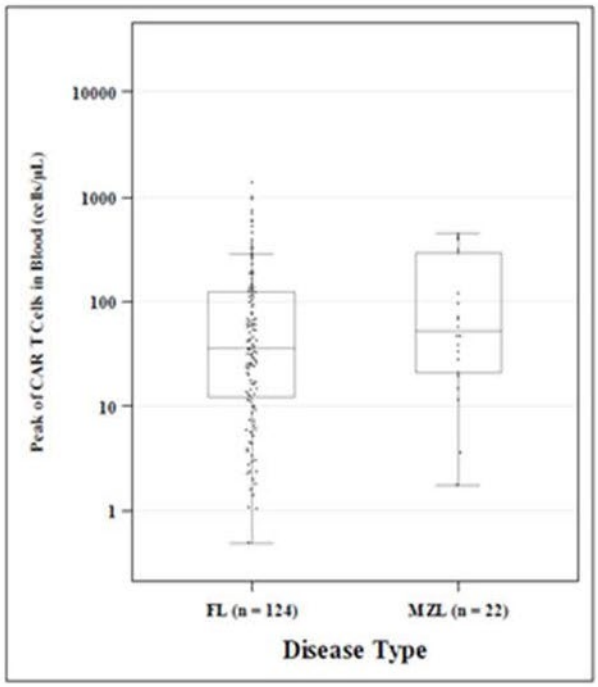


Figure 4. Peak and AUC0-28 of Number of Anti-CD19 CAR T Cells in Blood by Disease Type (Safety Analysis Set)





Pharmacokinetics in Special Populations and Subgroups

ZUMA-5 was not designed to test for differences between subgroups and formal comparisons were not prespecified. The statistical results of the subgroup analyses are descriptive in nature.

Age

Pediatric subjects were not enrolled. Among subjects with FL, 86 evaluable subjects were < 65 years of age and 38 subjects were ≥ 65 years of age. For subjects < 65 years of age, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 36.90 cells/µL (range: 1.05 to 1415.40 cells/µL) and 410.75 cells/µL•days (range: 10.91 to 1.99 x 10^4 cells/µL•days), respectively. For subjects ≥ 65 years of age, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 35.73 cells/µL (range: 0.49 to 1026.32 cells/µL) and 459.84 cells/µL•days (range: 5.93 to 7996.06 cells/µL•days), respectively. Anti-CD19 CAR T cells remain detectable at Month 12 in 65 of 85 subjects (52.42%) with evaluable samples at the time of the data cut-off date.

Gender

Among subjects with FL, 51 subjects were female and 73 subjects were male. For female subjects, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 37.62 cells/µL (range: 0.49 to 529.57 cells/µL) and 473.27 cells/µL•days (range: 5.93 to 5985.07 cells/µL•days), respectively. For male subjects, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 35.37 cells/µL (range: 1.05 to 1415.40 cells/µL) and 406.83 cells/µL•days (range: 10.91 to 1.99 x 104 cells/µL•days), respectively.

Race

Among subjects with FL, 115 subjects were white, 4 subjects were black or African American, 2 subjects were Asian, and 3 subjects self-reported their race as other. For white subjects, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 35.37 cells/µL (range: 0.49 to 1415.40 cells/µL) and 410.63 cells/µL•days (range: 5.93 to 1.99 x 104 cells/µL•days), respectively. In the 9 nonwhite subjects, peak anti-CD19 CAR T-cell levels ranged from 1.80 to 696.83 cells/µL, and AUC0-28 ranged from 23.61 to 5247.56 cells/µL•days.

Baseline tumor burden

Pharmacokinetic parameters were summarized by baseline tumor burden per central assessment. Tumor burden was measured as the sum of the cross product diameters of target lesions, ie, the sum of the products of the longest perpendicular diameters of tumors (SPD), per the International Working Group (IWG) Lugano Classification {Cheson 2014}. The association of anti-CD19 CAR T-cell expansion with baseline tumor burden was assessed according to quartiles of SPD as well as by median SPD. Among subjects with FL, median peak anti-CD19 CAR T-cell levels were 35.78 cells/μL in the first (lowest) tumor burden quartile, 60.13 cells/μL in the second quartile, 31.62 cells/μL in the third quartile, and 31.31 cells/μL in the fourth (highest) quartile. Median values for AUC0-28 were 422.37 cells/μL•days in the first quartile, 528.76 cells/μL•days in the second quartile, 364.55 cells/μL•days in the third quartile, and 249.73 cells/μL•days in the fourth quartile (Table 4).

Pharmacokinetic parameters were also summarized for subgroups of subjects with baseline tumor SPD ≤ median as compared to subjects with SPD > median (Table 5). For subjects with FL with SPD ≤ median, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 42.46 cells/μL (range: 1.08 to 1026.32 cells/μL) and 451.17 cells/μL•days (range: 19.08 to 7996.06 cells/μL•days), respectively. For subjects with SPD > median, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 31.46 cells/μL (range: 0.49 to 1415.40 cells/μL) and 331.09 cells/μL•days (range: 5.93 to 1.99 x 104 cells/μL•days), respectively.

Table 4. PK parameters by quartile of baseline tumor volume (SPD) (safety analysis set)

	Follicular Lymphoma (N = 124)			
	Q1:[Min = 289.2, Q1 = 1108.1] (N = 30)	Q2:(Q1 = 1108.1, Median = 2517.5] (N = 29)	Q3:(Median = 2517.5, Q3 = 4151.3] (N = 29)	Q4:(Q3 = 4151.3, Max = 34675.0] (N = 29)
AUC_{0-28} (cells/μL*days)				
n	30	29	29	29
Mean (STDEV)	1363.45 (2088.17)	921.14 (1157.51)	1417.86 (3682.67)	1155.98 (2190.66)
Median (Q1, Q3)	422.37 (149.58, 1145.67)	528.76 (143.63, 974.72)	364.55 (148.30, 985.64)	249.73 (68.29, 1254.93)
Min, Max	19.08, 7996.06	23.75, 4797.90	16.34, 1.99E+04	5.93, 1.02E+04
Peak (cells/μL)				
n	30	29	29	29
Mean (STDEV)	160.96 (271.09)	85.50 (94.31)	118.24 (268.53)	107.76 (208.54)
Median (Q1, Q3)	35.78 (11.27, 135.29)	60.13 (17.10, 127.34)	31.62 (13.05, 98.72)	31.31 (4.36, 117.93)
Min, Max	1.08, 1026.32	2.36, 341.61	1.59, 1415.40	0.49, 968.91
Time To Peak (Days)				
n	30	29	29	29
Mean (STDEV)	11.00 (3.67)	18.17 (36.08)	11.97 (5.88)	24.17 (66.87)
Median (Q1, Q3)	8 (8, 15)	13 (8, 15)	8 (8, 15)	9 (8, 15)
Min, Max	8, 17	8, 205	8, 29	8, 371

Data cutoff date = 12Mar2020

Table 5. PK parameters by median of baseline tumor volume (SPD) (safety analysis set)

	Follicular Lymphoma (N = 124)	
	SPD <= Median [a] (2517.5) (N = 59)	SPD > Median (2517.5) (N = 58)
AUC_{0-28} (cells/µL*days)		
n	59	58
Mean (STDEV)	1146.04 (1696.11)	1286.92 (3006.14)
Median (Q1, Q3)	451.17 (143.63, 1145.67)	331.09 (113.59, 1254.93)
Min, Max	19.08, 7996.06	5.93, 1.99E+04
Peak (cells/µL)		
n	59	58
Mean (STDEV)	123.87 (206.12)	113.00 (238.35)
Median (Q1, Q3)	42.46 (13.66, 130.63)	31.46 (8.61, 103.90)
Min, Max	1.08, 1026.32	0.49, 1415.40
Time To Peak (Days)		
n	59	58
Mean (STDEV)	14.53 (25.46)	18.07 (47.45)
Median (Q1, Q3)	9 (8, 15)	8 (8, 15)
Min, Max	8, 205	8, 371

Data cutoff date = 12Mar2020

Impact of concomitant use of tocilizumab and/or systemic corticosteroids

Among subjects with FL, 18 subjects (14.5%) received tocilizumab alone, 12 subjects (9.7%) received corticosteroids alone, 38 subjects (30.6%) received both tocilizumab and corticosteroids, and 56 subjects (45.2%) received neither tocilizumab nor corticosteroids. The timing and dose of corticosteroids administered following axicabtagene ciloleucel infusion were variable. Median peak anti-CD19 CAR T-cell levels and AUC0-28 were progressively higher in the following order: the lowest expansion was in subjects who received neither tocilizumab nor corticosteroids (peak: 21.38 cells/µL; AUC0-28: 221.28 cells/µL•days); similar expansion was observed in subjects who received either tocilizumab alone (peak: 25.71 cells/µL; AUC0-28: 373.54 cells/µL•days) or corticosteroids alone (peak: 29.64 cells/µL; AUC0-28: 468.05 cells/µL•days); the highest expansion was in subjects who received both tocilizumab and corticosteroids (peak: 120.39 cells/µL; AUC0-28: 1120.29 cells/µL•days).

B-cell levels (on-target off-tumor toxicity)

B cell levels were calculated as a percentage of CD19+, CD20+, or CD19+CD20+ B cells relative to viable CD45+ leukocytes in a flow cytometry assay. Among subjects with FL, 85 of 112 subjects (75.9%) in the safety analysis set had detectable B cells at baseline (enrollment/leukapheresis), with a median B cell level of 4.84% of viable leukocytes (range: 0.02% to 78.34%). At Month 3, the first time point at which B cells were measured after axicabtagene ciloleucel infusion, 41 of 102 subjects (40.2%) had detectable B cells, and the median B cell level declined to 0.47% (range: 0.02% to 47.35%). At Month 12, of 74 subjects 42 subjects (56.8%) with evaluable samples had detectable B cells (median: 6.53%, range: 0.03% to 48.49%). At Month 18, 24 of 35 subjects (68.57%) with evaluable samples had detectable B cells (median, 11.84%; range: 0.03% to 43.91%). At Month 24, 12 of 20 subjects (60.0%) with evaluable samples had detectable B cells (median, 9.05%; range: 0.14% to 46.06%).

Associations of PK with key efficacy and safety endpoints

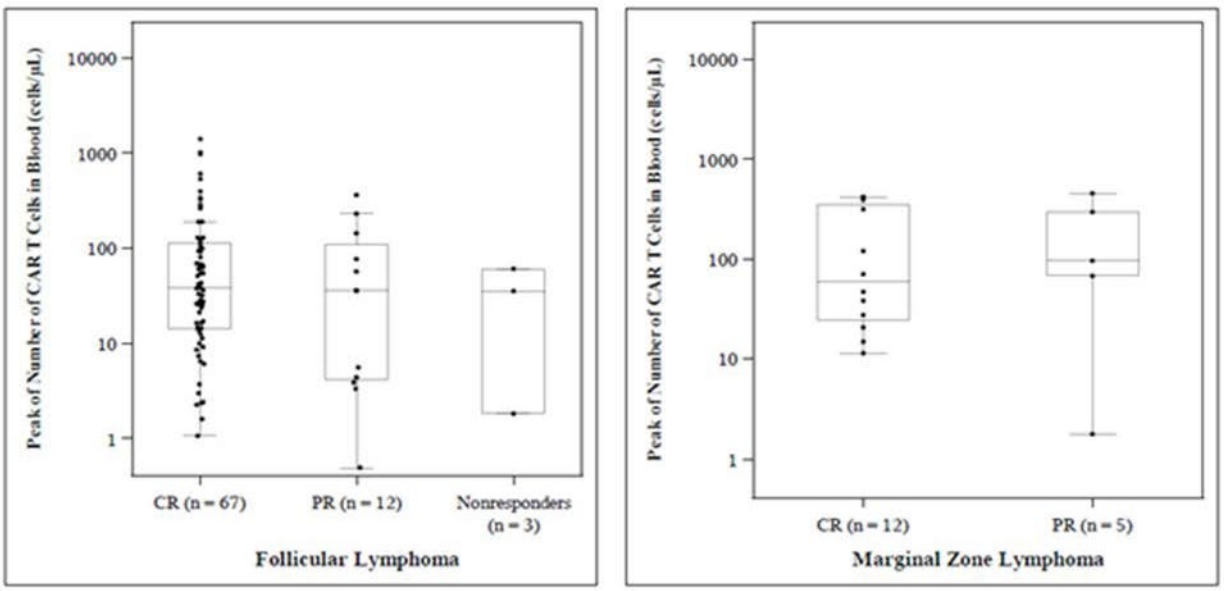
Objective Response

Among 84 subjects with FL in the inferential analysis set, 79 subjects (94.0%) had an objective response (CR or PR) and 3 subjects (3.6%) were nonresponders. One subject who had died prior to the first scheduled disease assessment was excluded from the analysis, and 1 subject was excluded due to undefined/no disease response by central assessment. Due to the limited number of nonresponders, no formal statistical comparisons were performed. The median peak anti-CD19 CAR T-cell levels in responders (n=112) versus nonresponders (n=5) were 38.0cells/µL (range: 0.49 to 1415.40 cells/µL) and 31.3 cells/µL (range: 1.80 to 60.24 cells/µL), respectively. The median AUC_{0-28} in responders versus nonresponders was 454.8 cells/µL•days (range: 5.93 to 1.99 x 104 cells/µL•days) and 247.14 cells/µL•days (range: 23.61 to 804.42 cells/µL•days), respectively.

Best Overall Response

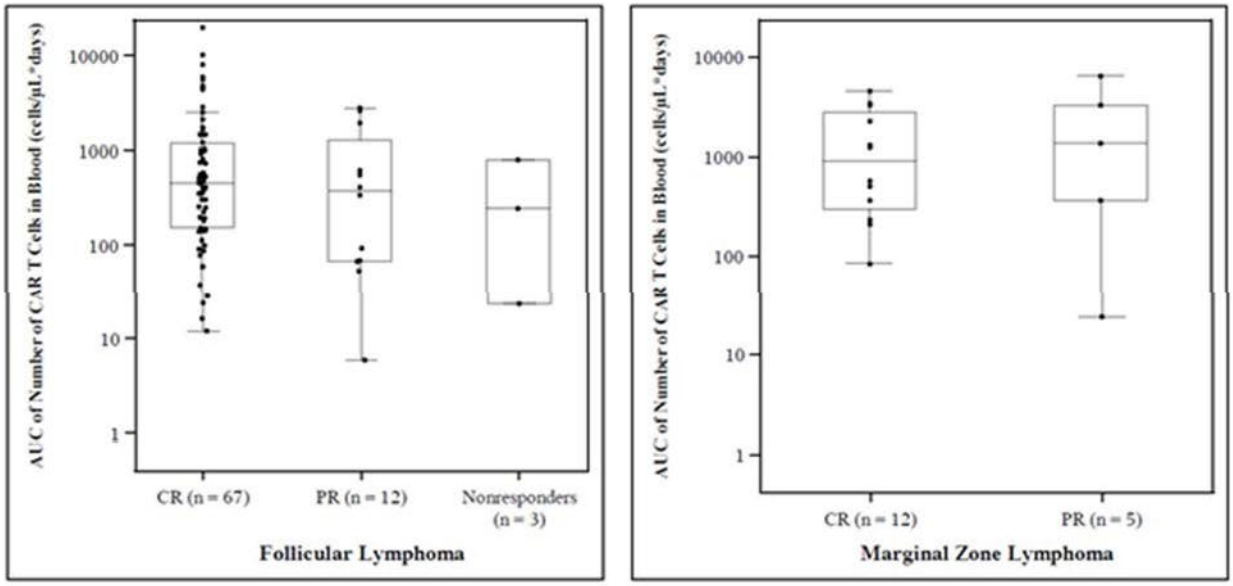
Among 84 evaluable subjects with FL, 67 subjects (79.8%) achieved a best response of CR, 12 subjects (14.3%) achieved PR, and 3 subjects (3.6%) were nonresponders per central read. Neither peak nor AUC0-28 were significantly different between the CR and PR groups. The median peak anti-CD19 CAR T-cell levels in subjects with CR versus PR were 38.33 cells/µL (range: 1.05 to 1415.40 cells/µL) and 35.78 cells/µL (range: 0.49 to 364.79 cells/µL), respectively (Wilcoxon rank sum nominal p = 0.4403). The median AUC0-28 in subjects with CR versus PR was 458.37 cells/µL•days (range: 12.00 to 1.99 x 104 cells/µL•days) and 374.12 cells/µL•days (range: 5.93 to 2800.43 cells/µL•days). In the nonresponder group, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 35.31 cells/µL (range: 1.80 to 60.24 cells/µL) and 247.14 cells/µL•days (range: 23.61 to 804.42 cells/µL•days), respectively.

Figure 5. Peak Number of Anti-CD19 CAR T Cells in Blood by Best Overall Response per Central Assessment (Inferential Analysis Set)



Data cutoff date = 12MAR2020.

Figure 6. AUC0-28 of Number of Anti-CD19 CAR T Cells in Blood by Best Overall Response per Central Assessment (Inferential Analysis Set)

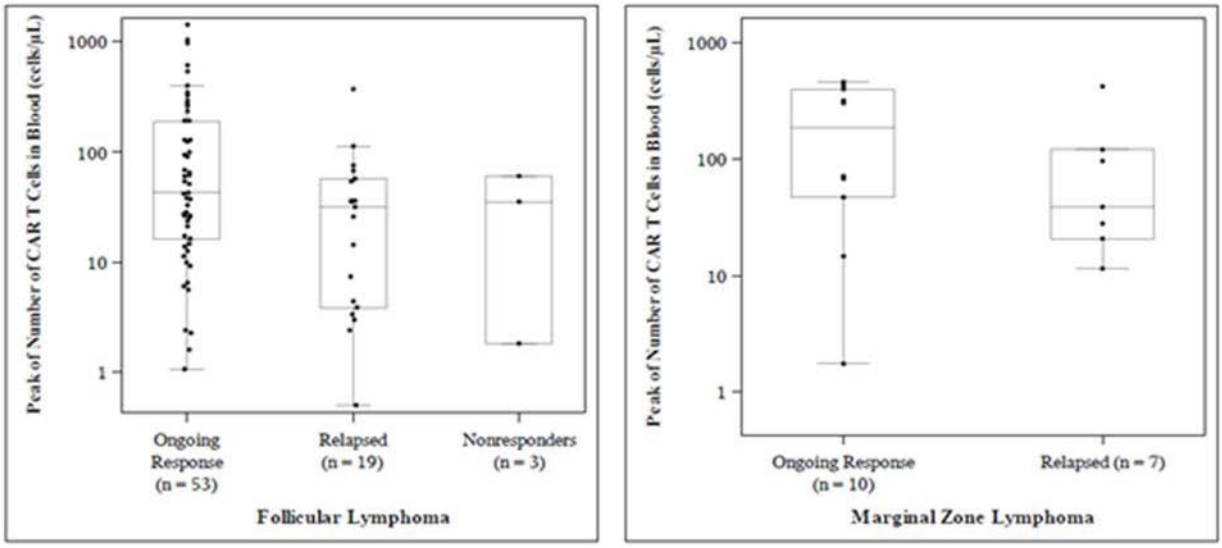


Data cutoff date = 12MAR2020.

Ongoing Response

Among 84 evaluable subjects with FL, 53 subjects (63.1%) were in ongoing response at the data cutoff date, 19 subjects (22.6%) had relapsed, and 3 subjects (3.6%) were nonresponders. Neither peak nor AUC0-28 were significantly associated with ongoing response, although a trend toward higher anti-CD19 CAR T-cell levels was observed in subjects with durable responses. The median peak anti-CD19 CAR T-cell levels in subjects with ongoing response versus relapse were 42.46 cells/µL (range: 1.05 to 1415.40 cells/µL) and 31.87 cells/µL (range: 0.49 to 364.79 cells/µL), respectively. The median AUC0-28 in subjects with ongoing response versus relapse was 473.27 cells/µL•days (range: 12.00 to 1.99 x 104 cells/µL•days) and 337.61 cells/µL•days (range: 5.93 to 2636.04 cells/µL•days), respectively. In the nonresponder group, the median peak anti-CD19 CAR T-cell level and AUC0-28 were 35.31 cells/µL (range: 1.80 to 60.24 cells/µL) and 247.14 cells/µL•days (range: 23.61 to 804.42 cells/µL•days), respectively.

Figure 7. Peak Number of Anti-CD19 CAR T Cells in Blood by Ongoing Response (Inferential Analysis Set)



Data cutoff date = 12MAR2020

Associations of PK with CRS and neurologic events

CRS

Among 124 evaluable subjects with FL, 8 subjects (6.5%) had Grade 3 or higher CRS and 116 subjects (93.5%) had Grade 2, Grade 1, or no CRS. The median peak anti-CD19 CAR T-cell level was 7.7-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2, Grade 1, or no CRS (272.99 vs 35.34 cells/µL; Wilcoxon rank sum nominal p = 0.0307). Similarly, the median AUC0-28 was 7.7-fold higher for subjects with Grade 3 or higher CRS compared with subjects with Grade 2, Grade 1, or no CRS (3155.66 vs 408.73 cells/µL•days; Wilcoxon rank sum nominal p = 0.0394).

Neurologic events

Among 124 evaluable subjects with FL, 19 subjects (15.3%) had Grade 3 or higher neurologic events, and 105 subjects (84.7%) had Grade 2, Grade 1, or no neurologic events. The median peak anti-CD19 CAR T-cell level was 3.7-fold higher for subjects with Grade 3 or higher neurologic events compared with subjects with Grade 2, Grade 1, or no neurologic events (122.85 vs 33.56 cells/µL; Wilcoxon rank sum nominal p = 0.0053). Similarly, the median AUC0-28 was 2.9-fold higher for subjects with Grade 3 or higher neurologic events compared with subjects with Grade 2, Grade 1, or no neurologic events (1145.67 vs 394.77 cells/µL•days; Wilcoxon rank sum nominal p = 0.0022).

Associations of product characteristics with PK

The following key characteristics showed potential associations ($p \leq 0.05$) with peak post-infusion levels of anti-CD19 CAR T cells:

- Percentage of Tnaïve cells
- (Tnaïve + Tcm)/(Tem + Teff) ratio
- Total number of Tnaïve cells infused

- Percentage of CCR7+ (Tnaïve + Tcm) cells

- Total number of CCR7+ T cells infused

- Percentage of CCR7− (Tem + Teff) cells

Table 6: Potential Associations of Post-infusion Peak Anti-CD19 CAR T-cell Levels in Blood With Product Characteristics (Safety Analysis Set: FL)

Product Characteristic	Number of Evaluable Subjects	Regression Coefficient (95% CI)	P-value
Transduction Rate (%)	124	-0.00 (-0.02, 0.02)	0.8073
IFN-gamma Level (pg/mL)	124	0.00 (-0.00, 0.00)	0.4560
CD4/CD8 Ratio	104	-0.03 (-0.13, 0.06)	0.5167
Tnaive (% of viable CD3+ cells)	105	0.02 (0.00, 0.04)	0.0466
Tcm (% of viable CD3+ cells)	105	0.01 (-0.02, 0.04)	0.4640
Tem (% of viable CD3+ cells)	105	-0.02 (-0.04, 0.00)	0.0849
Teff (% of viable CD3+ cells)	105	-0.01 (-0.03, 0.01)	0.2824
(Tnaive + Tcm)/(Tem + Teff) Ratio	105	0.25 (0.00, 0.50)	0.0466
Total Number of T Cells Infused (x 10^6)	124	0.00 (-0.00, 0.00)	0.3365
Total Number of Tnaive Cells Infused (x 10^6)	105	0.01 (0.00, 0.01)	0.0077
CCR7+ (Tnaive + Tcm) (%)	105	0.02 (0.00, 0.04)	0.0247
Total Number of CCR7+ T Cells Infused (x 10^6)	105	0.01 (0.00, 0.01)	0.0019
CCR7- (Tem + Teff) (%)	105	-0.02 (-0.04, -0.00)	0.0247

Data cutoff date = 12MAR2020

2.4.3. **Pharmacodynamics** (Serum)

Methods

Please refer to section 2.4.2.

Levels of key analytes (pro-inflammatory and immune-modulating cytokines, chemokines, and effector molecules) were to be evaluated in serum samples at multiple time points. Assays for 14 of the 17 key analytes have been qualified; assays for granzyme B, perforin and ferritin were performed in accordance to the manufacturer's recommended protocols. Analytes were to be measured at baseline (enrollment/leukapheresis), Day 0, and on Day 3, Day 7, Week 2, and Week 4 after axicabtagene ciloleucel infusion. The following 17 analytes (preselected from a larger panel of 40 analytes), which are known to be involved in mediation the antitumor activity of CAR T cells and treatment-related toxicities according to literature (*Kochendorffer 2017a; Neepalu 2017*) are presented:

- Homeostatic/proliferative: interleukin (IL)-15, IL-2, and IL-7

- Inflammatory/immune-modulating: C-reactive protein (CRP), interferon (IFN)-γ, IL-1 receptor antagonist (IL-1RA), IL-2 receptor alpha (IL-2Rα), IL-6, IL-10, and tumor necrosis factor (TNF)-α

- Chemokine: C-X-C motif chemokine (CXCL)10 and IL-8

- Immune effector: granzyme B and perforin

- Other analytes: ferritin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1

Results

IL-15

Serum IL-15 increased following the administration of the lymphodepleting chemotherapy regimen, as indicated by elevated levels of IL-15 at Day 0 relative to baseline. At baseline, the median IL-15 level was 2.10 pg/mL. At Day 0, following lymphodepleting chemotherapy, median IL-15 levels had increased approximately 14-fold to 28.90 pg/mL. Levels of IL-15 continued to rise after the infusion of axicabtagene ciloleucel, reaching a median peak value of 33.75 pg/mL. The median time to peak was 4 days after axicabtagene ciloleucel infusion. A 2-fold or higher change of IL-15 levels at the peak relative to baseline was observed in 122 of 124 subjects (98.4%) in the safety analysis set. At Week 4, median IL-15 levels declined to 4.10 pg/mL, with 65 of 118 subjects (55.1%) still demonstrating a 2-fold or higher change in the level of IL-15 relative to baseline.

IL-2

IL-2 levels in the serum increased rapidly after axicabtagene ciloleucel infusion in the safety analysis set. Median levels of IL-2 at baseline, Day 0, peak, and Week 4 were 0.90 pg/mL (imputed LLOQ), 0.90 pg/mL (imputed LLOQ), 3.05 pg/mL, and 0.90 pg/mL (imputed LLOQ), respectively. The median time to peak was 4 days after axicabtagene ciloleucel infusion. A 2-fold or higher change of IL-2 levels at the peak relative to baseline was observed in 79 of 124 subjects (63.7%) in the safety analysis set. At Week 4, median IL-2 levels generally returned toward baseline, with 2 of 118 subjects (1.7%) still demonstrating a 2-fold or higher change in the level of IL-2 over baseline.

IL-7

IL-7 increased following the administration of the lymphodepleting chemotherapy regimen, as indicated by higher levels of IL-7 at Day 0 relative to baseline. At baseline, the median IL-7 level was 14.85 pg/mL. At Day 0, following lymphodepleting chemotherapy, median IL-7 levels had increased approximately 2-fold to 27.75 pg/mL. Levels of IL-7 continued to rise after the infusion of axicabtagene ciloleucel, reaching a median peak value of 31.65 pg/mL. The median time to peak was 4 days after axicabtagene ciloleucel infusion. A 2-fold or higher change of IL-7 levels at the peak relative to baseline was observed in 69 of 124 subjects (55.6%) in the safety analysis set. At Week 4, median IL-7 levels declined toward baseline (17.45 pg/mL), with 10 of 118 subjects (8.5%) still demonstrating a 2-fold or higher change in the level of IL-7 relative to baseline.

CRP

Median serum levels of the acute phase reactant CRP in the safety analysis set at baseline, Day 0, peak, and Week 4 were 7.13 mg/L, 15.82 mg/L, 66.97 mg/L, and 0.54 mg/L, respectively. CRP appeared to be induced by lymphodepleting chemotherapy, with 64 of 120 subjects (52.9%) demonstrating a 2-fold or higher increase over baseline at Day 0. The median time to peak was 5 days after the infusion of axicabtagene ciloleucel. At the peak, 100 of 124 subjects (80.6%) demonstrated a 2-fold or higher change

of CRP levels over baseline. CRP levels generally decreased to baseline or below baseline at Week 4, with 6 of 118 subjects (5.1%) still demonstrating a 2-fold or higher change in the level of CRP over baseline at that time.

IFN-γ

Median serum levels of IFN-γ in the safety analysis set at baseline,Day 0, peak, and Week 4 were 7.50 pg/mL (imputed LLOQ), 7.50 pg/mL (imputed LLOQ),95.50 pg/mL, and 7.50 pg/mL (imputed LLOQ), respectively. The median time to peak was 7 days after infusion of axicabtagene ciloleucel. At the peak, 102 of 124 subjects (82.3%) demonstrated a 2-fold or higher change of IFN-γ levels over baseline. At Week 4, 40 of 118 subjects (33.9%) still demonstrated a 2-fold or higher change in the levels of IFN-γ over baseline.

TNF-α

Median levels of TNF-α in the safety analysis set at baseline, Day 0, peak, and Week 4 were 3.95 pg/mL, 2.30 pg/mL, 4.60 pg/mL, and 2.10 pg/mL, respectively. The median time to peak was 4 days after infusion of axicabtagene ciloleucel. At the peak, 20 of 124 subjects (16.1%) demonstrated a 2-fold or higher change of TNF-α levels over baseline. At Week 4, TNF-α levels generally returned toward baseline, with 3 of 118 subjects (2.5%) still demonstrating a 2-fold or higher increase of TNF-α over baseline.

CXCL10

Median levels of CXCL10 in the safety analysis set at baseline, Day 0, peak, and Week 4 were 343.75 pg/mL, 395.40 pg/mL, 1077.25 pg/mL, and 400.70 pg/mL, respectively. The median time to peak was 8 days after infusion of axicabtagene ciloleucel. At the peak, 72 of 124 subjects (58.1%) demonstrated a 2-fold or higher change of CXCL10 levels over baseline. At Week 4, 24 of 118 subjects (20.3%) still demonstrated a 2-fold or higher change in the levels of CXCL10 over baseline.

Granzyme B

Granzyme B in the safety analysis set at baseline, Day 0, peak, and Week 4 were 1.00 pg/mL (imputed LLOQ), 1.00 pg/mL (imputed LLOQ), 8.20 pg/mL, and 1.00 pg/mL (imputed LLOQ), respectively. The median time to peak was 8 days after infusion of axicabtagene ciloleucel. At the peak, 60 of 124 subjects (48.4%) demonstrated a 2-fold or higher change of granzyme B levels over baseline. At Week 4, granzyme B levels generally returned toward baseline, with 15 of 118 subjects (12.7%) still demonstrating a 2-fold or higher increase of granzyme B over baseline.

Summary of results

- After lymphodepleting chemotherapy treatment, median serum levels of CRP and IL-15 increased by at least 2-fold. Consistent with lymphodepletion, median serum levels of perforin decreased during this same time period.

- On Day 3 after infusion of axicabtagene ciloleucel, median serum levels of the majority of key analytes remained steady relative to baseline levels (< 2-fold change; CXCL10, granzyme B, ICAM-1, IL-1RA, IL 2Rα, IL-7, TNF-α, and VCAM-1) or were elevated by at least 2-fold relative to baseline (CRP, ferritin, IFN-γ, IL-2, IL-6, IL-8, IL-10, and IL-15).

- With the exception of perforin, the median time to peak for all key analytes was within 8 days after infusion of axicabtagene ciloleucel (range of medians: 4 to 8 days), coinciding with the peak anti-CD19 CAR T-cell expansion at 8 days; the median time to peak for perforin was 29 days, indicative of endogenous T-cell recovery. The majority of analytes increased by 2-fold or more at peak in ≥ 50% of subjects (exceptions: granzyme B, ICAM-1, perforin, TNF-α, and VCAM-1).

- By Week 4 after axicabtagene ciloleucel infusion, the majority of the 17 key serum analytes had returned to near baseline levels, ie, 5 analytes remained elevated by 2-fold or more in ≥ 20% of subjects (CXCL10, ferritin, IFN-γ, IL-6, and IL-15).

Associations of PD with CRS and neurologic events

Table 7. Potential Associations of Key Analytes With Safety Endpoints (Safety Analysis Set)

Analyte	Follicular Lymphoma		Marginal Zone Lymphoma	
	Grade 3 or Higher CRS	Grade 3 or Higher Neurologic Events	Grade 3 or Higher CRS[a]	Grade 3 or Higher Neurologic Events
CRP	No trend	No trend	NA	No trend
CXCL10	Positive	Positive[b]	NA	Inconclusive[c]
Ferritin	No trend	No trend	NA	No trend
Granzyme B	No trend	Positive	NA	No trend
ICAM-1	No trend	No trend	NA	No trend
IFN-γ	Positive	Positive	NA	No trend
IL-1RA	Positive	No trend	NA	No trend
IL-2	Positive	Positive	NA	No trend
IL-2Rα	Positive[b]	Positive	NA	No trend
IL-6	Positive	Positive	NA	No trend
IL-7	No trend	No trend	NA	No trend
IL-8	Positive[b]	Positive	NA	No trend
IL-10	Positive	Positive	NA	No trend
IL-15	No trend	Positive	NA	No trend
Perforin	No trend	No trend	NA	No trend
TNF-α	Positive[b]	Positive[b]	NA	No trend
VCAM-1	Positive[b]	No trend	NA	No trend

CRS

Of the 17 key analytes, the median peak serum levels for the following analytes were nominally higher among subjects with FL who experienced Grade 3 or higher CRS versus Grade 2, Grade 1, or no CRS after infusion of axicabtagene ciloleucel: CXCL10, IFN-γ, IL-1RA, IL-2, IL-2Rα, IL-6, IL-8, IL-10, TNF-α, and VCAM-1.

The 3 analytes with the lowest p-values for peak serum levels with Grade 3 or higher CRS compared with Grade 2, Grade 1, or no CRS were IL-2, TNF-α and IL-6. These were also the 3 analytes with the greatest fold change in median peak serum levels by grade of CRS.

Neurologic events

Of the 17 key analytes, the median peak serum levels for the following analytes were nominally higher among subjects with FL who experienced Grade 3 or higher neurologic events versus Grade 2, Grade 1, or no neurologic events after infusion of axicabtagene ciloleucel: CXCL10, granzyme B, IFN-γ, IL-2, IL-2Rα,

IL-6, IL-8, IL-10, IL-15, and TNF-α. These analytes also were associated with higher severity CRS with the exception of granzyme B and IL-15.

The 4 analytes with the lowest p-values for peak serum levels with Grade 3 or higher neurologic events compared with Grade 2, Grade 1, or no neurologic events were IFN-γ, IL-2, IL-6 and IL-10.

The 4 analytes with the greatest fold change in median peak serum levels by grade of neurologic events were IFN-γ, IL-6, IL-2 and Granzyme B.

Associations of B-cell levels with PK and disease response

Summary of results

Subjects with FL who were in ongoing response or whose disease had relapsed by DCO had numerically lower median B-cell levels at baseline compared with nonresponders (4.65% and 4.59% versus 11.45%, respectively).

Most subjects who were in ongoing response demonstrated B-cell aplasia at Month 3, with 28 of 44 subjects (63.6%) having B-cell levels below the LLOQ of the flow cytometry assay used for evaluation. B-cell levels slowly recovered by Month 18, with 5 of 13 subjects (38.5%) having B-cell levels below the LLOQ at that time.

Subjects in ongoing response who had B-cell aplasia (B-cell levels below the LLOQ) had numerically higher median CAR T-cell levels than subjects in ongoing response who did not have B-cell aplasia (B cells detectable) at all time points for which data exist, Month 3 to Month 18.

Anti-CD19 CAR T cells persisted at detectable levels (median CAR T-cell level: 0.01 cells/μL; range: < LLOQ to 0.93 cells/μL) in 8 subjects (61.5%) in ongoing response at Month 18 in the presence of recovered B-cell levels.

2.4.4. Discussion on clinical pharmacology

In general, the results presented on PK and PD and on measurable associations with both the drug product and the clinical parameters on safety and efficacy can be considered in line with current knowledge in the pharmacology of CAR T cell therapy. The observed variability in engraftment kinetics is known to be multifactorial (applied dose, conditioning therapy etc.), which might be an explanation for the observed differences within defined and between defined groups.

The relationship between axicabtagene ciloleucel exposure and clinical efficacy is obvious. Interestingly, in terms of OR rates, there seem to be no significant differences in the median peak anti-CD19 CAR-T cell levels between responders and non-responders in contrast to median AUC0-28 levels, whereas in terms of ongoing response, the differences in both median peak CAR T- cell levels and AUC0-28 are obvious.

Onset and severity of CRS and neurological events coincides with the kinetics of engraftment of axicabtagene ciloleucel and a rise in the concentration of cytokines in the serum. With regard to PK and the occurrence of CRS and/or neurological events, higher anti-CD19 CAR T-cell levels (peak and AUC_{0-28}) were associated with Grade 3 or higher CRS and neurological events, an observation, which is known according to scientific publications. Results presented on PD and clinical safety endpoints (CRS and neurological events) indicate a positive association of most of the 17 key cytokines, chemokines and immune effector molecules with higher grade CRS and neurological events, an observation, which is also in compliance with current scientific knowledge in the treatment with CAR T-cell products.

Nearly all patients, who experienced tumor response experienced concomitant elimination of non-malignant B-cells (on-target off-tumor toxicity). The figures on the loss of B-cells, associated with decrease in immunoglobulin concentrations as well as the figures on the return of B-cells at the subjects with FL in ZUMA-5 indicates to be consistent with literature data on CAR T cell therapy.

2.4.5. Conclusions on clinical pharmacology

The data provided are presented in a detailed and comprehensive way for the target indication r/r FL. The measurement methods used in ZUMA-5 are the commonly employed to track the CAR T cells after administration, and they appear to show viable correlations.

The results on PK and PD and on measurable associations with both the drug product and clinical outcome can be considered in line with current knowledge in the pharmacology of CAR T cell therapy.

2.5. Clinical efficacy

2.5.1. Main study

Title of Study

A Phase 2 Multicenter Study of Axicabtagene Ciloluecel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (ZUMA-5)

Methods

Study KTE-C19-105 is a Phase 2, multicenter, open-label study estimating the efficacy of axicabtagene ciloleucel in subjects with r/r iNHL.

Originally, approximately 50 subjects were planned to be enrolled and treated with cyclophosphamide and fludarabine conditioning chemotherapy, followed by a target dose of 2 x 10^6 autologous, genetically modified, anti-CD19 CAR T cells per kg body weight.

Each subject will proceed through the following study periods:

- Screening period
- Enrollment/Leukapheresis period
- Conditioning chemotherapy period
- Investigational product (IP) treatment period
- Post treatment assessment period
- Long-term follow-up period

Main inclusion criteria

- Histologically proven indolent NHL that is determined to be high risk as defined by one or more of the following criteria: Biopsy-proven progression of Grade 1, Grade 2, or Grade 3, a FL, within 24

months of original diagnosis of disease that was subsequently treated with first-line anti-CD20 monoclonal antibody- and cytotoxic agent-containing combination chemoimmunotherapy (eg, R-CHOP, R-Bendamustine, R-CVP, R-fludarabine)

OR

Progression of Grade 1, Grade 2, or Grade 3,a FL, or other iNHL (excluding small lymphocytic lymphoma) within 6 months of completion of second or greater line therapy with anti-CD20 monoclonal antibody- and alkylating agent-containing chemoimmunotherapy

OR

Progression of Grade 1, Grade 2, or Grade 3 a FL, or other iNHL at any point following autologous transplantation

- At least 1 measurable lesion according to the revised IWG Response Criteria for Malignant Lymphoma (Cheson 2007). Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy MRI of the brain showing no evidence of CNS lymphoma
- ECOG performance status of 0 or 1
- MRI of the brain showing no evidence of CNS lymphoma
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function

Main exclusion criteria

- Transformed FL
- Small lymphocytic lymphoma
- Histological Grade 3b FL
- Known presence of lymphoma cells in the peripheral blood
- History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (eg, cervix, bladder, breast) unless disease-free and without anticancer therapy for at least 3 years
- Autologous stem cell transplant within 6 weeks of planned axicabtagene ciloleucel infusion
- History of allogeneic stem cell transplantation
- Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for retreatment
- Prior CAR therapy or other genetically modified T-cell therapy

As per protocol amendment 2 (19 Jan 2018), the main inclusion criterion with regard to eligible iNHL histology was revised to limit histologically proven B-cell iNHL to the FL (Grade 1, 2 or 3a) or MZL nodal or extranodal histological subtypes based on the WHO 2016 classification and to remove primary relapse and relapse after ASCT high risk categories of iNHL. An additional inclusion criterion was added to require relapse or refractory disease after 2 or more prior lines of therapy and that prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent (Single agent anti-CD20 antibody was not counted as line of therapy for eligibility). Additionally, it was clarified that stable disease (without relapse) > 1 year from completion of last therapy is not eligible. Furthermore, the inclusion criterion with the requirement of having at least 1 measurable lesion was updated to include the more recent Lugano Response Criteria for Malignant Lymphoma (Cheson et al, 2014). And finally, the requirement for MRI of

the brain to show there is no evidence of CNS lymphoma was removed and replaced by a requirement of having no known history or suspicion of central nervous system (CNS) involvement by lymphoma.

Diagnosis of FL or MZL for determination of study eligibility was made by the investigator at each site. Diagnosis was centrally confirmed retrospectively on archival tumor tissue by NeoGenomics Laboratories (Irvine, CA). The retrospective review of central diagnosis included assessment of CD19 expression. Demonstration of CD19 expression was not required for study eligibility. Tumor tissue in the form of an archival formalin-fixed paraffin embedded block, pre-cut slides, or an on-study baseline (prior to lymphodepletion) biopsy, were to be submitted for the central review.

Study participants

Adult patients with r/r follicular lymphoma (FL) and marginal zone lymphoma (MZL)

Treatments

Lymphodepletion (days-5 through -3 before infusion with axicabtagene ciloleucel)

The 3-day conditioning regimen of fludarabine and cyclophosphamide is described below. Hydration for cyclophosphamide may alternatively be performed according to local institutional guidelines.

- IV hydration with 1 L of 0.9% NaCl given prior to cyclophosphamide on the day of infusion followed by:
- Cyclophosphamide 500mg/m2 IV over 60 minutes followed by:
- Fludarabine 30mg/m2 IV over 30 minutes followed by:
- An additional 1L of 0.9% NaCl at the completion of the cyclophosphamide infusion
- Add Mesna per institutional guidelines

Axicabtagene Ciloleucel Premedication Dosing

The following pre axicabtagene ciloleucel infusion medications should be administered approximately 1 hour prior to infusion.

- Tylenol 650 mg PO
- Benadryl (12.5 mg IV or 25 mg PO)

Axicabtagene Ciloleucel (Day 0 after Fludarabine and Cyclophosphamide)

Subjects will receive axicabtagene ciloleucel treatment consisting of a single infusion of CAR transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (1.0 x 10^6 anti-CD19 CAR T cells/kg to 2.4 x 10^6 anti-CD19 CAR T cells/kg). For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti-CD19 CAR T cells will be administered.

Toxicity management

- Tocilizumab and corticosteroids in accordance to recommendations
- Alternatives allowed, such as anti-IL-6 antibodies (siltuximab) anti-TNF-alpha monoclonal antibody (infliximab), soluble TNF-alpha receptor (etanercept), and IL-1- receptor antagonist (anakinra)
- Vasopressors

Vasopressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin + norepinephrine equivalent of ≥ 10 µg/min*
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min*

- Prophylactic anti-epileptics (e. g. levetiracetam) allowed
- Gammaglobulin according institutional guidelines

Axicabtagene Ciloleucel retreatment

Subjects who achieve a response of PR or better at the 3-month disease assessment, but subsequently experience disease progression, had the option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel.

The following criteria must be met to be considered for a repeat course of therapy:

- Subject has at least PR or CR at the Month 3 disease assessment, but subsequently experienced progression of disease at a later time.
- CD19 expression on tumor cells confirmed locally by biopsy after disease progression and prior to treatment
- Subject continues to meet the original study eligibility criteria with the exception of prior axicabtagene ciloleucel use in this study. Screening assessments should be repeated if clinically indicated, as determined by the investigator, to confirm eligibility**.**
- Subject has not received subsequent therapy for the treatment of lymphoma.
- Subject did not experience Grade 4 CRS, Grade 4 neurological event, or any other life-threatening toxicity during the original course of treatment.
- Toxicities related to conditioning chemotherapy (fludarabine and cyclophosphamide), with the exception of alopecia, have resolved to ≤ Grade 1 or returned to baseline prior to retreatment.
- Subject does not have known neutralizing antibodies (exception: if a non-neutralizing KTE-C19 antibody develops, subject may be retreated if he or she meets the original study eligibility criteria).

Outcomes/endpoints

Primary endpoint

Objective response rate (ORR), defined as complete response (CR)+ partial response (PR) per Lugano classification and central assessment

Key secondary endpoints

- Progression-free survival (PFS), including the 12-month PFS rate (central/investigator assessment)
- ORR for those subjects who had 3 or more lines of prior therapy per central assessment

- DOR (central/investigator assessment
- Overall Survival (OS)
- Incidence of AEs
- PD and PK

Sample size

Up to approximately 160 subjects, including up to approximately 125 subjects with FL with at least 80 subjects with FL in the inferential analysis set, were to be enrolled and treated. The trial used a single-arm design to estimate the ORR in subjects with r/r iNHL treated with axicabtagene ciloleucel.

The primary analysis was to be performed when at least 80 subjects in the FL inferential analysis set had had the opportunity to be followed for 12 months after the first disease assessment. The primary efficacy endpoint for this study in the inferential analysis set had 93% power to reject the null hypothesis that the ORR was 40% given the ORR was 60%, with a 1-sided alpha level of 0.0237.

The analysis sets have been revised after the first round of questions by the Applicant as follows, excluding centrally confirmed non-FL:

FAS with 3 or more lines of prior therapy: n=75

IAS with 3 or more lines of prior therapy: n=55

SAS with 3 or more lines of prior therapy: n=73

Randomisation and Blinding (masking)

The study was a single arm, open-label trial and subjects and investigators were aware of treatment received. Data handling procedures for the study were to be devised to reduce potential sources of bias and maintain the validity and credibility of the study. These procedures were to be outlined in the study statistical analysis plan, DSMB charter, and trial integrity document.

Statistical methods

Analysis sets

The following analysis sets were defined:

- Inferential Analysis Set (IAS): all enrolled subjects (FL or MZL) treated with any dose of axicabtagene ciloleucel who met the eligibility criteria. This analysis set was to be used as primary efficacy analysis set.
- Full Analysis Set (FAS): all enrolled (leukapheresed) subjects; this set was to be used for sensitivity analyses.
- Safety Analysis Set: all subjects treated with any dose of axicabtagene ciloleucel; the safety analysis set was used for all safety analyses.
- Retreatment Analysis Set: all subjects who underwent retreatment with axicabtagene ciloleucel; this set was used for all retreatment safety and efficacy analyses. Subjects in the re-treatment analysis set were not included in any other analysis sets.

Statistical Hypotheses

Four hypotheses were tested using a fixed sequence procedure in terms of ORR and CR rate as determined by central review to control the overall type I error at 1-sided alpha level of 0.025 with the following testing order:

- Hypothesis 1 (H1): ORR as determined by central review less than 40% in subjects with FL in the IAS
- Hypothesis 2 (H2): CR rate as determined by central review less than 15% in subjects with FL in the IAS
- Hypothesis 3 (H3): test for ORR as determined by central review less than 40% in subjects with FL in the IAS who had had 3 or more lines of prior therapy
- Hypothesis 4 (H4): test for CR rate as determined by central review less than 15% in subjects with FL in the IAS who had had 3 or more lines of prior therapy

Hypotheses H1 through H4 were to be assessed at the time of the interim analyses 3, 4, and 5 and at the time of the primary analysis. No formal hypothesis testing was planned for the MZL histological subtype. The analysis is descriptive only.

Historical control ORR and CR rates

The historical control rate for ORR was estimated based on results of limited available data on the approved therapies for r/r FL after 2 or more prior lines of therapy. These approved therapies at the time of trial design were the PI3K inhibitors idelalisib and copanlisib. In the trial of idelalisib, the ORR and CR rate for patients with relapsed FL after 2 or more prior lines of therapy were 54% and 8%, respectively, and in the trial of copanlisib, the ORR and CR rate for patients with r/r FL after 2 or more prior lines of therapy were 59% and 14%, respectively. It was anticipated that most subjects would have had prior treatment with at least one of the aforementioned PI3K inhibitors; thus, an ORR <40% or CR rate <15% would not be of clinical interest. Therefore, these rates were used for hypothesis testing.

Analyses of primary and secondary endpoints

The subject incidence of objective response and complete response together with 2-sided 95% confidence intervals were to be calculated with the Clopper-Pearson method. An exact binomial test was to be used to compare the ORR and CR per central read among the subjects with FL and among the subjects with FL who have had 3 or more lines of prior therapy to the hypothesized historical control rates of 40% and 15%, respectively.

Kaplan-Meier plots, estimates, and 2-sided 95% confidence intervals were to be generated for DOR, PFS and OS. Kaplan-Meier estimates were to be provided for the proportion of subjects who were alive and progression-free at 3-month time intervals. The number of subjects censored or having had events was to be summarized, as well as the reasons for censoring and the event type (PD or death; if applicable).

The reverse Kaplan-Meier approach (Schemper and Smith 1996) was to be used to estimate the follow-up time for DOR.

Planned analyses

Five interim analyses were planned. An independent data and safety monitoring board (DSMB) was to be chartered to make trial conduct recommendations based on an analysis of risk versus benefit. The 5 interim analyses were as follows:

- Interim analysis 1 was to be conducted after 10 subjects in the safety analysis set had been enrolled and treated with axicabtagene ciloleucel and had had an opportunity to be followed for 4 weeks. This analysis was to be for safety only.
- Interim analysis 2 was to be conducted after 30 subjects in the safety analysis set had been enrolled and treated with axicabtagene ciloleucel and had had an opportunity to be followed for 4 weeks. This analysis was to be for safety only.
- Interim analysis 3 was to be performed when 30 subjects in the FL inferential set had had the opportunity to be followed for 6 months after the axicabtagene ciloleucel infusion. This interim analysis was to be for safety and to assess early demonstration of efficacy.
- Interim analysis 4 was to be performed when 80 subjects in the FL inferential analysis set had had the opportunity to be followed for 6 months after axicabtagene ciloleucel infusion.
- Interim analysis 5 was to be performed when at least 80 subjects with FL in the inferential analysis set had had the opportunity to be followed for 9 months after the first disease response assessment.
- The primary analysis was to be performed when at least 80 subjects with FL in the inferential analysis set have had the opportunity to be followed for 12 months after the first disease response assessment.

Additionally the following updated analyses were planned:

- Follow-up analysis 1 was planned to be performed when 80 subject in the FL inferential analysis set have had the opportunity to be followed for 18 months after axicabtagene ciloleucel infusion. This analysis was to be for safety and efficacy and was to be descriptive.
- Follow-up analysis 2 was planned to be performed when 80 subjects in the FL inferential analysis set have had the opportunity to be followed for 24 months after axicabtagene ciloleucel infusion. This analysis was to be for safety and efficacy and was to be descriptive.
- The final analysis was to occur after all subjects have completed the study.

It should be noted that subjects with MZL were included in the fifth interim analysis and the primary analysis if they had had the opportunity to undergo the Week 4 disease assessment.

An alpha spending function was to be used to allocate the alpha level between interim analyses 3, 4, and 5, and the primary analysis. Using the O'Brien-Fleming boundary of the Lan-DeMets family of alpha spending functions, the nominal 1-sided alpha used to test for efficacy at interim analyses 3 was 0.0003.With Protocol Amendment 5 the remaining alpha was split for interim analyses 4, 5 and primary analysis as 0.0005, 0.0005, and 0.0237.

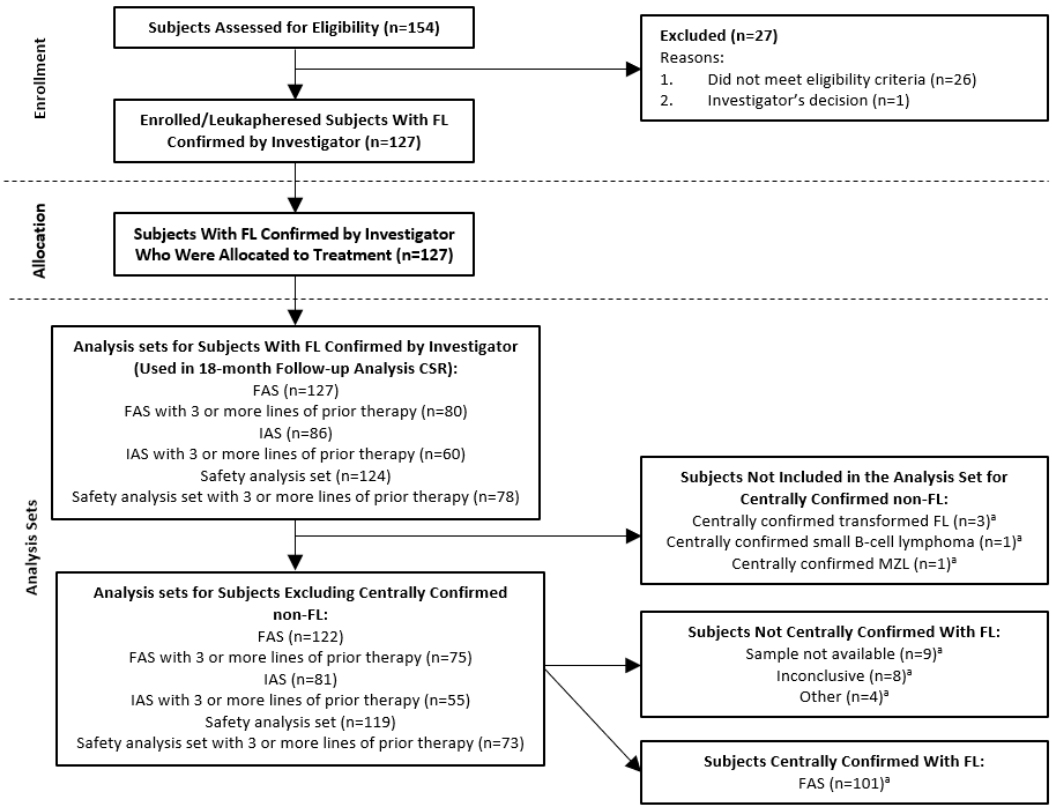
Multiplicity control over endpoints

If the criteria for early efficacy were met for H1, the same alpha spending function was to be applied to test H2 at this interim analysis; otherwise, H2 through H4 was not be tested until the subsequent analysis. If the criteria for early efficacy were met for H1 and H2, the same alpha spending function was to be applied to test H3; otherwise, H3 and H4 were not to be tested until the subsequent analysis. If the criteria for early efficacy were met for H1, H2, and H3, the same alpha spending function was to be applied to test H4; otherwise, H4 was not be tested until the subsequent analysis. The study was not to be stopped if early efficacy was demonstrated.

Results

Participant flow

Figure 8. Participant flow



Recruitment

In total, 154 subjects with iNHL were assessed for eligibility.

Among these 154 subjects, 127 subjects were diagnosed with FL according to local histopathological assessment. Although central confirmation of diagnosis was retrospective and was not required for treatment or continued enrolment on the study per protocol and statistical analysis plan (SAP), the number of enrolled subjects with histologic confirmation of FL by central assessment was 101 subjects in the FAS. For the majority of the 26 subjects for which local diagnosis of FL could retrospectively not be confirmed per central assessment ("inconclusive"/"other"), this was due to the following: 1) the protocol did not mandate that the same tissue specimens had to be reviewed by local and central review pathologists, 2) the majority of the non-confirmed FL by central assessment were due to insufficient tissue, and 3) insufficient tumor in the samples provided. Only for 5 of the 26 subjects central lab assessment was highly suggestive of an alternative non-FL diagnosis (3 subjects with transformed FL, 1 subject with small B-cell lymphoma, and 1 subject with MZL per central assessment). These 5 subjects were subsequently excluded from the FAS.

Among subjects with FL (subjects with centrally confirmed non-FL excluded), the full analysis set (FAS) comprised 122 subjects. Of these subjects, 119 were included in the safety analysis set, 81 were included

in the inferential analysis set, 75 were included in the subset of subjects with 3 or more lines of prior therapy in the FAS. No additional subjects were enrolled/treated after the primary analysis data cutoff date.

No manufacturing failures occurred. The median time from leukapheresis to the products release from the manufacturing site was 12.0 days (range: 10 to 37 days). Axicabtagene ciloleucel was delivered to the study site a median of 17.0 days (range: 13 to 72 days) after leukapheresis and was administered to the subject a median of 27.0 days (range: 19 to 330 days) after leukapheresis. Delays that occurred (> 50 days) from manufacturing of the product to delivery to the clinical site or from leukapheresis to infusion of the product were due to the clinical course of the disease.

Conduct of the study

On June 2017, the first subject was screened in this study and the first subject was enrolled on 20 Jun 2017. The data cutoff date for the primary analysis (12-month follow-up) was 12 March 2020. The data cut-off date of the 18-month follow-up analysis, also included in the submission, was 14 September 2020. The data cut-off date of the 24 month follow-up analysis, provided at the time of Day 120 responses and the data to be presented in the SmPC, is 31 March 2021.

Study protocol amendments

The original protocol, dated 26 November 2016, was amended 5 times before the data cutoff date of the primary analysis of the study. The amendments made related to iNHL in general and/or MZL/FL in particular.

Study protocol deviations

In the safety analysis set (SAS), important protocol deviations (IPDs) were reported for 23 subjects (19%) during the course of the trial. Most of IPDs were missing data (n=20; 16%).

Baseline data

Table 8. Demographics and Baseline Characteristics in FAS and IAS of Subjects With FL or of Subjects With FL Who Received 3 or More Lines of Prior Therapy (Excluding Centrally Confirmed Non-FL; based on 24 months analyses, DCO 31 Mar 2021)

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N = 81)	FL With 3 or More Lines of Prior Therapy (N = 55)
Age (years)				
n	122	75	81	55
Mean (STDEV)	58.9 (9.8)	59.8 (9.1)	59.4 (10.5)	59.8 (9.8)
Median (Q1, Q3)	60.0 (53.0, 67.0)	60.0 (54.0, 67.0)	62.0 (53.0, 69.0)	62.0 (54.0, 69.0)
Min, Max	34, 79	34, 79	34, 79	34, 79
Age category - n (%)				
< 65 Years	85 (70)	52 (69)	53 (65)	37 (67)

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N = 81)	FL With 3 or More Lines of Prior Therapy (N = 55)
>= 65 Years	37 (30)	23 (31)	28 (35)	18 (33)
Sex - n (%)				
Male	73 (60)	47 (63)	46 (57)	35 (64)
Female	49 (40)	28 (37)	35 (43)	20 (36)
Ethnicity - n (%)				
Hispanic or Latino	6 (5)	4 (5)	4 (5)	4 (7)
Not Hispanic or Latino	116 (95)	71 (95)	77 (95)	51 (93)
Missing	0 (0)		0 (0)	0 (0)
Race - n (%)				
Asian	3 (2)	3 (4)	2 (2)	2 (4)
Black or African American	3 (2)	1 (1)	2 (2)	1 (2)
White	113 (93)	70 (93)	76 (94)	51 (93)
Other	3 (2)	1 (1)	1 (1)	1 (2)
Country - n (%)				
United States	112 (92)	67 (89)	77 (95)	51 (93)
France	10 (8)	8 (11)	4 (5)	4 (7)
ECOG performance status, n (%)				
0	77 (63)	44 (59)	49 (60)	32 (58)
1	45 (37)	31 (41)	32 (40)	23 (42)
Histologically diagnosed disease type per local lab, n (%)				
FL	122 (100)	75 (100)	81 (100)	55 (100)
FL histological category at study entry, n (%)				
Grade 1	32 (26)	22 (29)	18 (22)	11 (20)
Grade 2	61 (50)	38 (51)	41 (51)	30 (55)
Grade 3a	29 (24)	15 (20)	22 (27)	14 (25)
Disease stage[f], n (%)				
I	5 (4)	3 (4)	2 (2)	2 (4)
II	13 (11)	7 (9)	9 (11)	6 (11)

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N = 81)	FL With 3 or More Lines of Prior Therapy (N = 55)
III	46 (38)	34 (45)	35 (43)	25 (45)
IV	58 (48)	31 (41)	35 (43)	22 (40)
FLIPI total score[g], n (%)				
0	4 (3)	2 (3)	3 (4)	2 (4)
1	18 (15)	9 (12)	10 (12)	7 (13)
2	48 (39)	30 (40)	32 (40)	20 (36)
3	34 (28)	22 (29)	23 (28)	17 (31)
4	15 (12)	11 (15)	11 (14)	8 (15)
5	3 (2)	1 (1)	2 (2)	1 (2)
Low risk (0 - 1)	22 (18)	11 (15)	13 (16)	9 (16)
Intermediate risk (2)	48 (39)	30 (40)	32 (40)	20 (36)
High risk (3 - 5)	52 (43)	34 (45)	36 (44)	26 (47)
Relapsed/refractory subgroup[a], n (%)				
Relapsed	40 (33)	17 (23)	23 (28)	12 (22)
Refractory	82 (67)	58 (77)	58 (72)	43 (78)
Double refractory subgroup[a], n (%)				
Yes	36 (30)	18 (24)	28 (35)	17 (31)
No	86 (70)	57 (76)	53 (65)	38 (69)
Number of prior lines of therapy[e], n (%)				
1	3 (2)	–	–	–
2	43 (35)	–	26 (32)	–
3	30 (25)	30 (40)	17 (21)	17 (31)
4	25 (20)	25 (33)	20 (25)	20 (36)
≥ 5	20 (16)	20 (27)	18 (22)	18 (33)
n	121	75	81	55
Mean (STDEV)	3.31 (1.59)	4.16 (1.47)	3.58 (1.59)	4.33 (1.40)
Median (Q1, Q3)	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)
Min, Max	1.0, 10.0	3.0, 10.0	2.0, 9.0	3.0, 9.0
Response to last line of therapy, n (%)				

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N = 81)	FL With 3 or More Lines of Prior Therapy (N = 55)
Complete response	34 (28)	17 (22)	21 (26)	11 (20)
Partial response	24 (20)	11 (15)	15 (19)	8 (15)
Stable disease	22 (18)	19 (25)	17 (21)	16 (29)
Progressive disease	23 (19)	16 (21)	16 (20)	11 (20)
Not evaluable	4 (3)	4 (5)	3 (4)	3 (5)
Unknown	14 (11)	8 (11)	9 (11)	6 (11)
Receiving prior autologous stem cell transplant, n (%)				
Yes	30 (25)	22 (29)	21 (26)	16 (29)
No	92 (75)	53 (71)	60 (74)	39 (71)
Time to relapse from first anti-CD20-chemotherapy combination therapy[b], n (%)	121	75	81	55
≥ 24 months	41 (34)	31 (41)	29 (36)	22 (40)
< 24 months	65 (54)	38 (51)	44 (54)	29 (53)
High tumor bulk as defined by GELF criteria[c], n (%)	63 (52)	43 (57)	40 (49)	30 (55)
Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm	31 (25)	24 (32)	22 (27)	19 (35)
Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm	22 (18)	17 (23)	16 (20)	13 (24)
Presence of B symptoms	8 (7)	4 (5)	5 (6)	3 (5)
Splenomegaly	22 (18)	14 (19)	15 (19)	10 (18)
Pleural effusions or peritoneal ascites	5 (4)	4 (5)	2 (2)	2 (4)
Cytopenias	15 (12)	11 (15)	9 (11)	8 (15)
Leukemia	1 (1)	0 (0)	0 (0)	0 (0)
Prior PI3K inhibitor, n (%)				
Yes	32 (26)	30 (40)	24 (30)	22 (40)
No	90 (74)	45 (60)	57 (70)	33 (60)
Prior anti-CD20 + alkylating agent, n (%)				
Yes	121 (99)	75 (100)	81 (100)	55 (100)
No	1 (1)	0 (0)	0 (0)	0 (0)

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N = 81)	FL With 3 or More Lines of Prior Therapy (N = 55)
Prior lenalidomide, n (%)				
Yes	34 (28)	28 (37)	23 (28)	20 (36)
No	88 (72)	47 (63)	58 (72)	35 (64)
Bone marrow assessment at baseline[d], n (%)				
Lymphoma present	34 (28)	24 (32)	19 (23)	15 (27)
Lymphoma present but not FL	1 (1)	1 (1)	1 (1)	1 (2)
Lymphoma not present	86 (70)	50 (67)	61 (75)	39 (71)
Unknown	1 (1)	–	–	–

a. Subjects with iNHL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Subjects with iNHL who progressed > 6 months of completion of the most recent prior treatment are defined as relapsed.
b. Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. Number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on number of subjects who ever received anti-CD20-chemotherapy combination therapy.
c. Disease burden, as defined by any of Groupe d Etude des Lymphomes Folliculaires (GELF) criteria (subject meets the criteria for high tumor bulk versus subject does not meet the criteria for high tumor bulk): Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm, Any nodal or e xtranodal tumor mass with a diameter of ≥ 7 cm, B symptoms, Splenomegaly, Pleural effusions or peritoneal ascites, Cytopenias, or Leukemia.
d. Bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/ bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.
e. Prior anti-CD20 single agent includes rituximab, ofatumumab, obinutuzumab.

Retrospective Analysis of Tumor CD19 Status

Among 122 subjects with FL in the FAS excluding centrally confirmed non-FL, 113 subjects were with available samples at baseline; of these, 95 subjects had confirmed $CD19^+$ antigen status, 8 subjects had confirmed $CD19^-$ status, and 10 subjects' CD19 antigen status were missing/inconclusive at baseline.

Outcomes and estimation

Primary analysis (DCO 12 Mar 2020)

Among the 84 subjects with FL (per investigator assessment) in the IAS who had the opportunity to be followed for 12 months after the first disease response assessment, the ORR was 94% (79/84 subjects), with a 95% CI of (87%, 98%). This ORR was significantly greater ($p < 0.0001$; less than the alpha level of 0.0237 allocated at the primary analysis) than the prespecified historical control rate of 40%. Therefore, the null hypothesis was rejected and the primary efficacy endpoint for ZUMA-5 was met (Hypothesis 1).

The CR rate was 80% (67/84 subjects, 95% CI: 70%, 88%), which was significantly greater ($p < 0.0001$) than the prespecified control rate of 15%. Therefore, the null hypothesis was rejected and the criteria for the key secondary endpoint of CR rate was met (Hypothesis 2).

Among the 58 subjects with FL who had 3 or more lines of prior therapy, the ORR was 95% (55 of 58 subjects, 95% CI: 86%, 99%), with a CR rate of 81% (47 of 58 subjects, 95% CI: 69%, 90%). The ORR of 95% was significantly greater ($p < 0.0001$) than the prespecified control rate of 40%; therefore, the

criteria for efficacy for the secondary endpoint of ORR in subjects who had 3 or more lines of prior therapy was met (Hypothesis 3).

The CR rate among subjects with FL who had 3 or more lines of prior therapy was tested because the ORR among these subjects was significant. The CR rate of 81% was significantly greater ($p < 0.0001$) than the prespecified control rate of 15%; therefore, the criteria for efficacy for the secondary endpoint of CR rate in subjects who had 3 or more lines of prior therapy was met (Hypothesis 4).

24 month FU analysis (DCO 31 Mar 2021)

Based on the 24-month data cutoff date, the ORR and CR rate of subjects with FL who received 3 or more lines of therapy in the FAS and IAS excluding centrally confirmed non-FL were similar (ORR: 91% versus 95% respectively; CR rate: 77% versus 78%, respectively). Among the subjects with FL who received 3 or more lines of therapy in the FAS excluding centrally confirmed non-FL and who achieved a CR or PR, the median time to first objective response was 0.99 month (range: 0.8 to 3.1 months). Among the 58 subjects who achieved a CR, the median time to first CR was 1.05 month (range: 0.8 to 12.1 months). Twenty nine out of 75 FL patients who had 3 or more prior lines of therapy initially achieved a PR, 19 of whom later achieved CR. The KM median estimates of DOR, PFS, OS, and TTNT in the FAS and IAS were similar (DOR: 38.6 months in each analysis set; PFS: 40.2 versus 28.0 months, respectively; OS: not estimable in each analysis set; TTNT: 40.2 versus 39.6 months, respectively). The pattern of the KM PFS plots in the FAS and IAS are parallel. Median follow-up time for DOR was 22.6 months (95% CI: 18.8, 23.0 months).

Table 9.Summary of Key Efficacy Results of Subjects With FL Who Received 3 or More Lines of Prior Therapy Excluding Centrally Confirmed Non-FL (FAS and IAS); DCO 31Mar2021

	FAS		IAS	
	FL (N = 122)	FL With 3 or More Lines of Prior Therapy (N = 75)	FL (N =81)	FL With 3 or More Lines of Prior Therapy (N = 55)
ORR (95% CI[a]); p-value	92% (85%, 96%);	91% (82%, 96%);	94% (86%, 98%); p < 0.0001	95% (85%, 99%); p < 0.0001
CR (95% CI[a]); p-value	77% (69%, 84%);	77% (66%, 86%)	78% (67%, 86%); p < 0.0001	78% (65%, 88%); p < 0.0001
PR (95% CI[a])	15% (9%, 22%)	13% (7%, 23%)	16% (9%, 26%)	16% (8%, 29%)
DOR[b]				
KM Median (95% CI) (months)	38.6 (NE, NE)	38.6 (24.7, NE)	38.6 (24.7, NE)	38.6 (22.7, NE)
KM estimate of proportion in response at 24 months (95% CI)	71.0 (60.3, 79.3)	67.6 (52.7, 78.7)	68.1 (55.5, 77.8)	62.8 (46.9, .75.2)
PFS[c]				
KM Median (95% CI) (months)	40.2 (28.9, NE)	40.2 (26.6, NE)	39.6 (25.7, NE)	28.0 (23.5, NE)
KM estimate of proportion progression-free at 24 months (95% CI)	71.9 (62.4, 79.5)	71.8 (58.6, 81.4)	65.1 (53.0, 74.9)	61.3 (46.0, 73.5)
OS[c]				
KM Median (95% CI) (months)	NE (40.2, NE)	NE (40.2, NE)	NE (39.6, NE)	NE (39.6, NE)
KM estimate of proportion alive at 24 months (95% CI)	87.9 (80.3, 92.7)	85.5 (74.6, 91.9)	81.3 (71.0, 88.3)	79.8 (66.5, 88.3)
TTNT[c]				
KM Median (95% CI) (months)	40.2 (40.2, NE)	40.2 (26.6, NE)	39.6 (28.0, NE)	39.6 (22.8, NE)
KM estimate of proportion event-free at 24 months (95% CI)	70.8 (61.7, 78.1)	67.0 (54.8, 76.6)	64.0 (52.6, 73.4)	59.7 (45.5, 71.3)

Figure 9. KM Plot of DOR Per central Assessment of Subjects With FL and OR Who received 3 or More Lines of Therapy (FAS Excluding centrally Confirmed Non-FL)

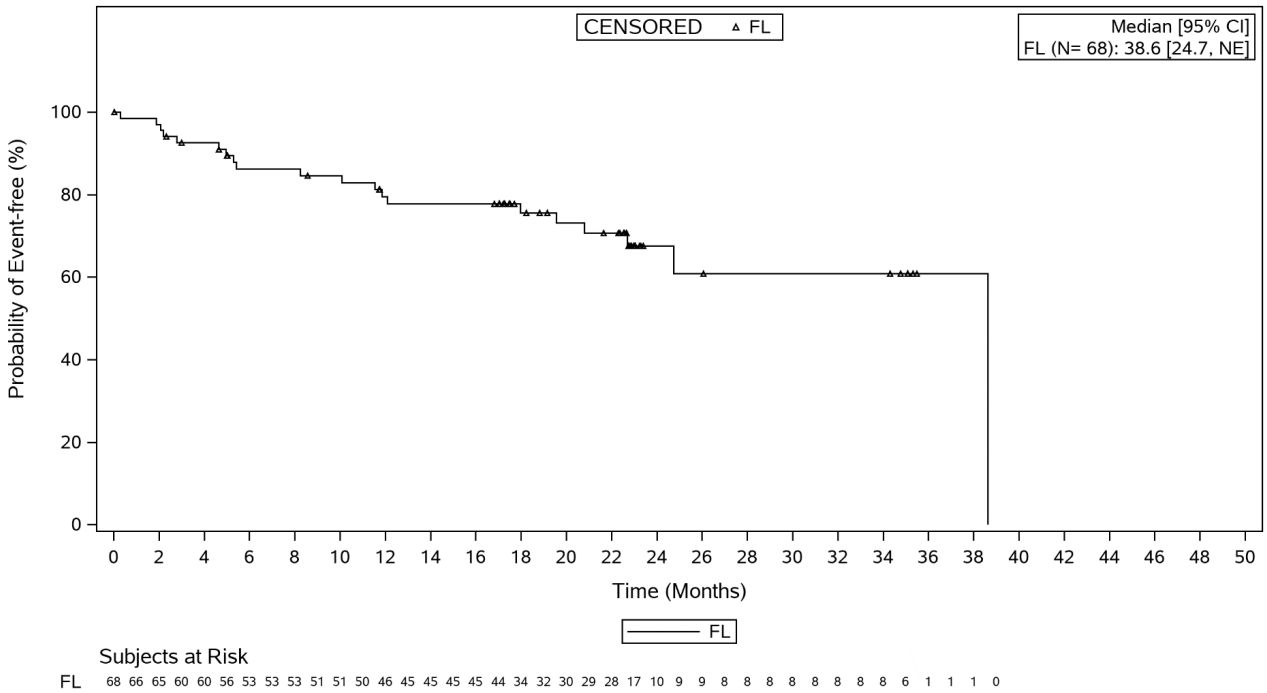


Figure 10. KM Plot of PFS Per Central Assessment of Subjects With FL Who Received 3 or More Lines of Prior Therapy (FAS Excluding Centrally Confirmed Non-FL)

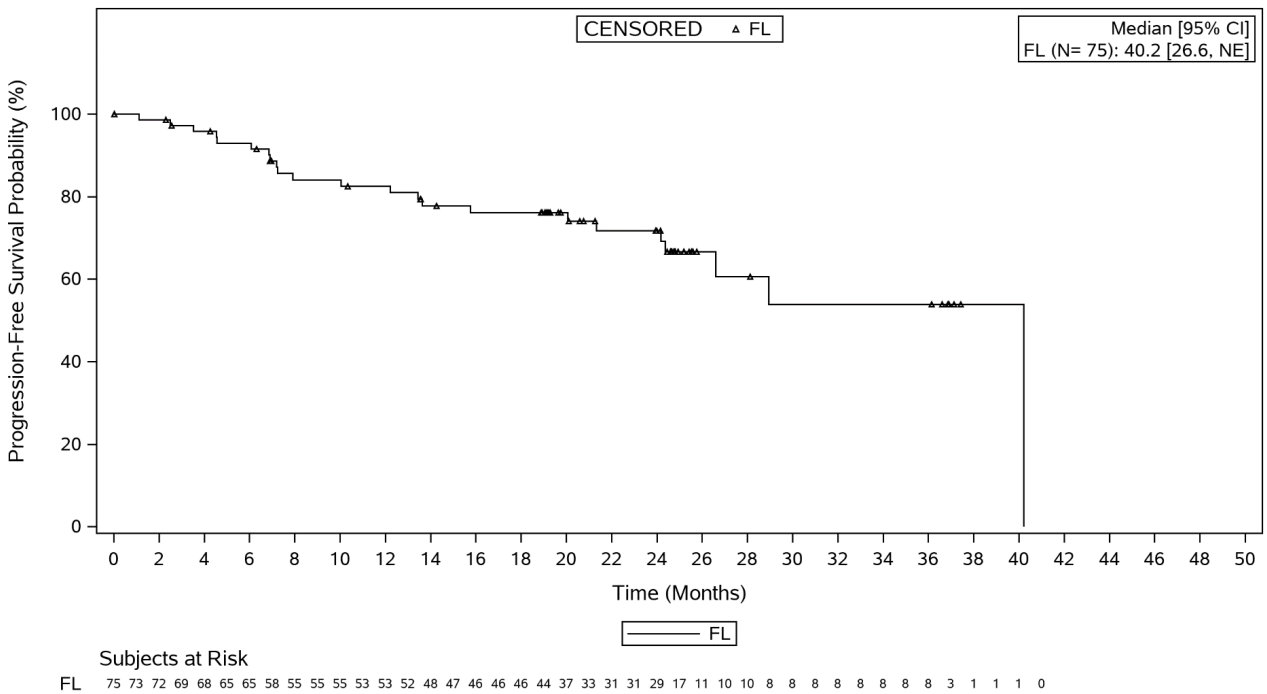
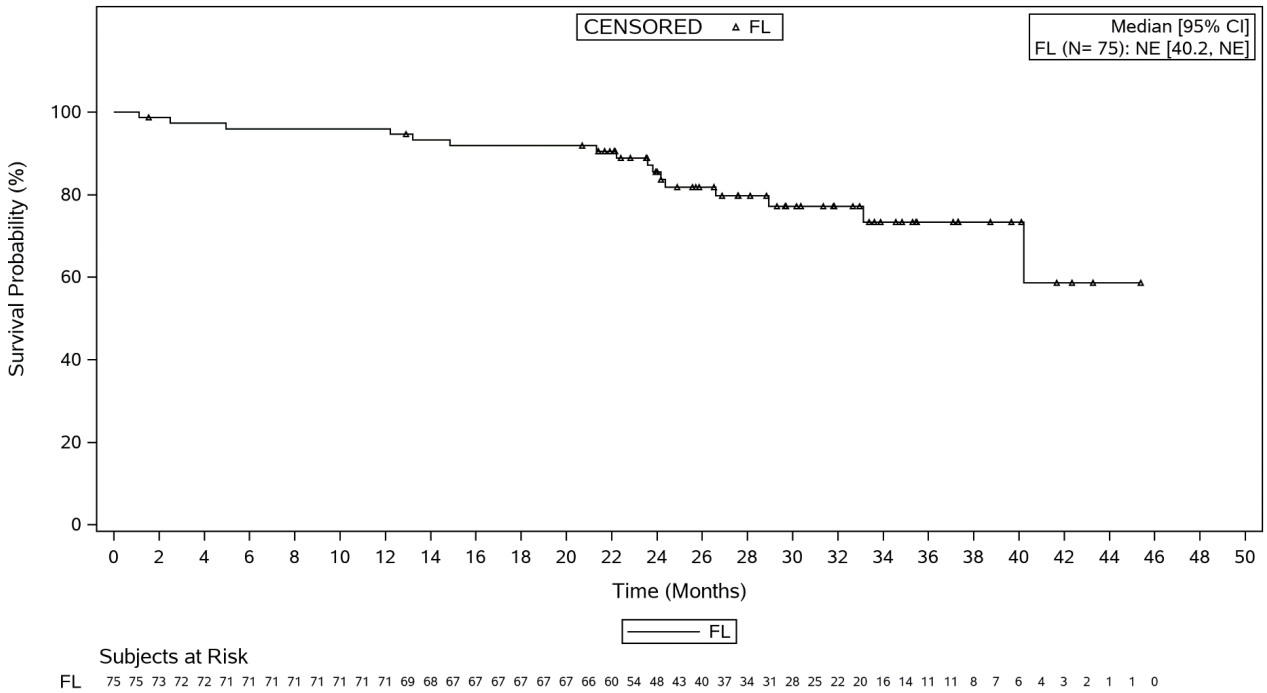


Figure 11. KM Plot of OS of Subjects With FL Who Received 3 or More Lines of Prior Therapy (FAS Excluding Centrally Confirmed Non-FL)



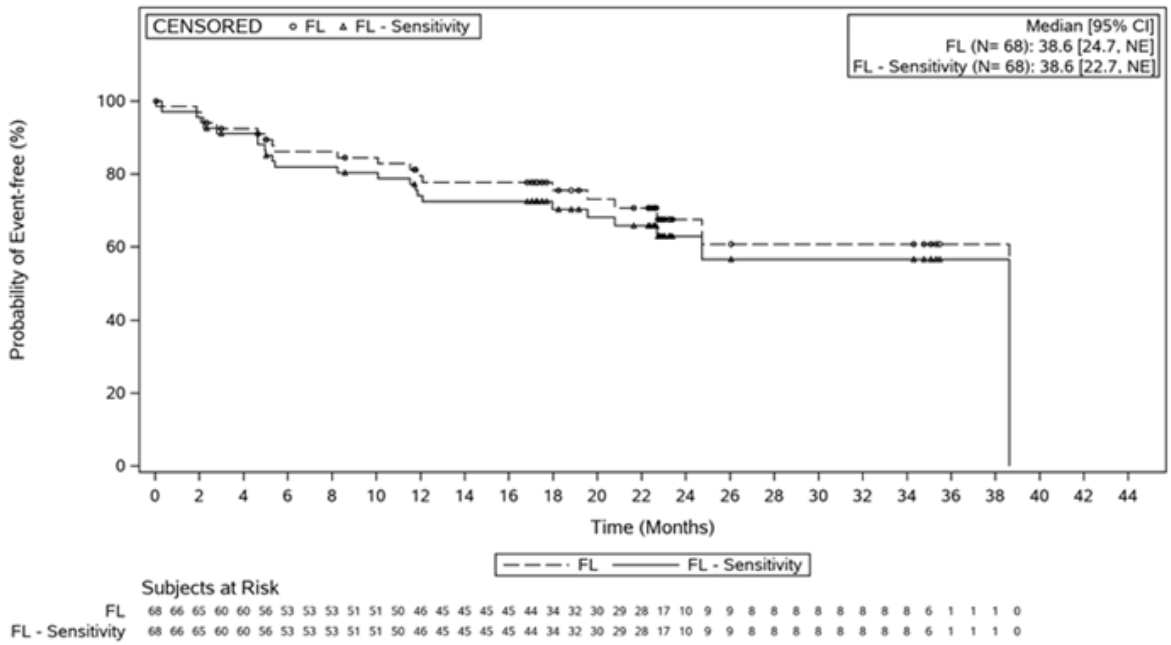
Ancillary analyses (based on 24 months analysis; CDO 31 MAR 2021)

Sensitivity analyses for DOR and PFS according to EMA censoring rules (FAS with FL subjects who received ≥ 3 prior lines of therapy, excluding centrally confirmed non-FL)

In the primary analysis for DOR based on the 24-months data cut-off date, 3 subjects were censored due to starting new anticancer therapy and 1 subject due to retreatment. In the primary analysis for PFS, 4 subjects were censored due to starting new anticancer therapy and 2 subjects due to retreatment. These subjects started new anticancer therapy or retreatment in the absence of prior documented progression confirmed by central assessment, however the decision to start another treatment or to retreat was based on the investigator's assessment reporting disease progression. All subjects who received subsequent HSCT had disease progression reported by both central and investigator's assessment. Upon request, sensitivity analyses for DOR and PFS in the FL FAS excluding centrally confirmed non-FL who received ≥ 3 prior lines of therapy, considering the start of other new anticancer therapies or axi-cel retreatment in the absence of prior documented progression as an event (EMA censoring rules), were provided.

Response to retreatment

Figure 12. KM Plot of DOR Per Central Assessment – Sensitivity Analysis with New Anticancer Therapy and Retreatment as Event in Subjects with Objective Response and 3 or more prior lines of therapy (FAS Excluding Centrally Confirmed Non-FL)



Data cutoff date = 31MAR2021

Table 10. PFS Per Central Assessment Based on Primary Analysis Versus Sensitivity Analysis With New Anticancer Therapy and Retreatment as Event (FAS Excluding Centrally Confirmed Non-Follicular Lymphoma, Subjects with 3 or More Lines of Prior Therapy)

	Primary Analysis[a] (N = 75)	Sensitivity Analysis[b] (N = 75)
Number of subjects	75	75
Events, n (%)	23 (31)	29 (39)
Censored, n (%)	52 (69)	46 (61)
KM Median (95% CI) PFS time (months)	40.2 (26.6, NE)	28.9 (24.2, NE)
Min, Max PFS time (months)	0.0, 40.2	0.0, 40.2
Events		
Disease progression, n (%)	14 (19)	14 (19)
Death from any cause, n (%)	9 (12)	9 (12)
Started new anticancer therapy, n (%)	–	4 (5)[e]
Retreatment, n (%)	–	2 (3)
Censoring reason		
Response ongoing, n (%)	42 (56)[c]	42 (56)
Lost to follow-up, n (%)	1 (1)	1 (1)
Withdrawal of consent, n (%)	1 (1)	1 (1)
Investigator decision, n (%)	1 (1)	1 (1)
Stem cell transplant, n (%)	0 (0)	0 (0)
Response assessed but no disease, n (%)	1 (1)	0 (0)
Response not yet assessed, n (%)	1 (1)[d]	1 (1)
Started new anticancer therapy, n (%)	4 (5)[e]	–
Retreatment, n (%)	2 (3)[f]	–
Progression-free rate % (95% CI) by KME		
3 Month	97.2 (89.3, 99.3)	94.5 (86.1, 97.9)
6 Month	92.9 (83.7, 97.0)	90.4 (80.9, 95.3)
9 Month	83.8 (72.6, 90.7)	77.7 (66.3, 85.7)
12 Month	82.3 (70.8, 89.5)	76.3 (64.7, 84.6)
15 Month	77.2 (65.0, 85.6)	70.5 (58.4, 79.7)
18 Month	75.2 (62.5, 84.1)	69.0 (56.8, 78.4)
24 Month	71.0 (55.9, 81.7)	65.0 (52.3, 75.2)
Median (95% CI) follow-up time (months) (reverse KM approach)	18.8 (15.9, 19.4)	24.6 (21.3, 25.2)

Data cutoff date = 31MAR2021.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11. Summary of Efficacy for ZUMA-5		
Title: A Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL)		
Study identifier	KTE-C19-105	
Design	Phase II, multicenter, open-label, study in adults with r/r B-cell iNHL of FL or MZL	
	Duration:	After completing anti-CD19 CAR T-cell infusion, all subjects will be followed in the post-treatment assessment period counting from Day 0 to Month 3 visit
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	After Month 3 visit, all treated subjects will be followed in a long-term follow-up period for survival and disease status. The duration of the study is planned to be up to 15 years.
Hypothesis	The hypothesis is that the ORR of subjects with FL or subjects with FL and 3 or more prior lines of therapy, determined by central assessment, to axicabtagene ciloleucel was significantly higher than the pre-specified historical ORR of 40% and the CR rate of subjects with FL or subjects with FL and 3 or more prior lines of therapy, determined by central assessment, to axicabtagene ciloleucel was significantly higher than the pre-specified historical CR rate of 15%.	
Treatments groups (per DCO 31 March 2021 = 24 months analysis)	FL in the FAS	<u>Subjects with FL (based on ZUMA-5 24-month Follow-up CSR Addendum):</u> Number enrolled (ie, underwent leukapheresis): n = 127 Number treated: n = 124 Median actual follow-up[a]: 26.55 months (range: 0.3 to 44.3 months) Median potential follow-up[b]: 28.80 months (range: 18.2 to 44.3 months)
		Subjects with FL and 3 or more prior lines of therapy <u>(based on ZUMA-5 24-month Follow-up CSR Addendum)</u>: Number enrolled (ie, underwent leukapheresis): n = 80 Number treated: n = 78 Median actual follow-up[a]: 26.55 months (range: 0.3 to 44.3 months) Median potential follow-up[b]: 28.81 months (range: 19.9 to 44.3 months)
		<u>Subjects with FL excluding centrally confirmed non-FL (based on Kite's newly proposed analysis set):</u> Number enrolled (ie, underwent leukapheresis): n = 122 Number treated: n = 119 Median actual follow-up[a]: 25.86 months (range: 0.3 to 44.3 months) Median potential follow-up[b]: 28.52 months (range: 18.2 to 44.3 months)
		Subjects with FL and 3 or more prior lines of <u>excluding centrally confirmed non-FL (based on Kite's newly proposed analysis set)</u>: Number enrolled (ie, underwent leukapheresis): n = 75 Number treated: n = 73 Median actual follow-up[a]: 26.55 months (range: 0.3 to 44.3 months) Median potential follow-up[b]: 28.06 months (range: 19.9 to 44.3 months)

Endpoints and definitions	Primary endpoint	ORR in subjects with FL	ORR was defined as the incidence of CR or PR using central assessment per the Lugano Classification {Cheson 2014}
	Secondary endpoints	ORR in subjects with FL and 3 or more prior lines of therapy	ORR in subjects with 3 or more prior lines of therapy is defined as the incidence of a CR or a PR by the Lugano Classification {Cheson 2014} as determined by central assessment for those subjects who had 3 or more lines of prior therapy.
		CR rate in subjects with FL and 3 or more prior lines of therapy	CR rate in subjects with 3 or more prior lines of therapy is defined as the incidence of CR as best response to treatment by the Lugano Classification {Cheson 2014} as determined by central assessment for those subjects who had 3 or more lines of prior therapy.
		DOR	DOR was defined as the time from first objective response (CR or PR) to disease progression or death. Subjects not meeting the criteria by the analysis data cutoff date were censored at their last evaluable disease assessment date prior to the data cutoff date or new anticancer therapy start date (including SCT or retreatment of axicabtagene ciloleucel), whichever was earlier
		PFS	PFS was defined as the time from the axicabtagene ciloleucel infusion date (analyses based on the IAS and the safety analysis set) or the enrollment/leukapheresis date (analysis based on the FAS) to the date of disease progression per {Cheson 2014} or death due to any cause. The main analysis of PFS was based on progression defined per central assessment. PFS for subjects who received any subsequent anticancer therapy (including SCT or retreatment with axicabtagene ciloleucel) in the absence of prior documented progression was censored at the date of the last evaluable disease assessment prior to subsequent anti-cancer therapy or the last evaluable disease assessment prior to SCT.
		OS	OS was defined as the time from the axicabtagene ciloleucel infusion for the analyses based on the IAS and the safety analysis set or the enrollment/leukapheresis date for the analysis based on the FAS to the date of death due to any cause.
		TTNT[c]	TTNT is defined as the time from the leukapheresis date (for FAS) or the axicabtagene ciloleucel infusion date (for IAS and safety analysis set) to the start of subsequent anticancer therapy or death from any cause. Subjects who had not received subsequent anticancer therapy, or were still alive by the data cutoff date, or had died after the data cutoff date were to be censored at their last new therapy status date prior to the data cutoff date. Subjects who were alive after the data cutoff date were to be censored at the data cutoff date.
Database lock	For the primary analysis: 12 March 2020 For the 18-month follow-up: 14 September 2020 For the 24-month follow-up: 31 March 2021		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population	FAS and IAS in subjects with FL or in subjects with FL and 3 or more prior lines of therapy excluding centrally confirmed non-FL		

and time point description					
Descriptive statistics and estimate variability	**Treatment group**	**FL in FAS**	**FL with 3 or more prior lines of therapy in FAS**	**FL in IAS**	**FL with 3 or more prior lines of therapy in IAS**
	Number of subjects (N)	122	75	79	53
	ORR (CR+PR) n (%), [95% CI per the Clopper-Pearson Method]	111 (91), [84, 95]	68 (91), [82, 96]	74 (94), [86, 98]	50 (94), [84, 99]
	CR n (%), [95% CI per the Clopper-Pearson Method]	92 (75), [67, 83]	58 (77), [66, 86]	62 (78), [68, 87]	42 (79), [66, 89]
	DOR median in months, [95% CI]	NE [NE, NE]	NE [20.8, NE]	NE [20.8, NE]	NE [20.8, NE]
	PFS median in months, [95% CI]	NE [NE, NE]	NE [24.2, NE]	NE [23.5, NE]	NE [23.5, NE]
	OS median in months, [95% CI]	NE [NE, NE]	NE [NE, NE]	NE [23.5, NE]	NE [23.5, NE]

Effect estimate per comparison	ORR in subjects with FL in the IAS	Comparison groups	ORR in subjects with FL versus 40% historic ORR
		P-value	< 0.0001
	ORR in subjects with FL and 3 or more prior lines of therapy in the IAS	Comparison groups	ORR in subjects with FL and 3 or more prior lines of therapy versus 40% historic ORR
		P-value	< 0.0001
	CR rate in subjects with FL in the IAS	Comparison groups	CR in subjects with FL versus 15% historic CR rate
		P-value	< 0.0001
	CR rate in subjects with FL and 3 or more prior lines of therapy in the IAS	Comparison groups	CR rate in subjects with FL and 3 or more prior lines of therapy versus 15% historic CR rate
		P-value	< 0.0001

Notes	Results presented above are from analyses in the FAS and IAS in subjects with FL or in subjects with FL and 3 or more prior lines of therapy excluding centrally confirmed non-FL using the central assessment of disease based on the Lugano Classification {Cheson 2014}.				
Analysis description	**24-month Follow-up Analysis**				
Analysis population and time point description	FAS and IAS in subjects with FL or in subjects with FL and 3 or more prior lines of therapy excluding centrally confirmed non-FL				
Descriptive statistics and estimate variability	**Treatment group**	**FL in FAS**	**FL with 3 or more prior lines of therapy in FAS**	**FL in IAS**	**FL with 3 or more prior lines of therapy in IAS**
	Number of subjects (N)	122	75	81	55
	ORR (CR+PR) n (%), [95% CI per the Clopper-Pearson Method]	112 (92), [85, 96]	68 (91), [82, 96]	76 (94), [86, 98]	52 (95), [85, 99]
	CR n (%), [95% CI per the Clopper-Pearson Method]	94 (77), [69, 84]	58 (77), [66, 86]	63 (78), [67, 86]	43 (78), [65, 88]
	DOR median in months, [95% CI]	38.6 [NE, NE]	38.6 [24.7, NE]	38.6 [24.7, NE]	38.6 [22.7, NE]
	PFS median in months, [95% CI]	40.2 [28.9, NE]	40.2 [26.6, NE]	39.6 [25.7, NE]	28.0 [23.5, NE]
	OS median in months, [95% CI]	NE [40.2, NE]	NE [40.2, NE]	NE [39.6, NE]	NE [39.6, NE]
	TTNT[c] median in months, [95% CI]	40.2 [40.2, NE]	40.2 [26.6, NE]	39.6 [28.0, NE]	39.6 [22.8, NE]
Notes	Results presented above are from analyses in the FAS and IAS in subjects with FL or in subjects with FL and 3 or more prior lines of therapy excluding centrally confirmed non-FL using the central assessment of disease based on the Lugano Classification {Cheson 2014}.				

a Actual follow-up time was calculated as (death date or last date known live – the axicabtagene ciloleucel infusion date + 1)/30.4375.

b Potential follow-up time was calculated as (the data cutoff date – the axicabtagene ciloleucel infusion date +

1)/30.4375.

c TTNT was added after the primary analysis.

Supportive study

As supportive study (external control) served the SCHOLAR-5 trial.

Title

A comparison of clinical outcomes from ZUMA-5 and the internal SCHOLAR-5 external control cohort in r/r FL (grades 1-3A).

Trial design

A multicenter, international observational retrospective study based on EMR and clinical trial data.

Objectives

- To describe clinical and demographic characteristics and treatment patterns in patients with r/r iNHL in the real-world setting, who would be eligible for CAR-T.
- To estimate overall response rate (ORR) among patients with r/r iNHL in the real-world setting. complete response (CR), Partial Response (PR), Overall survival (OS), duration of response (DoR), progression-free survival (PFS) and time to next treatment (TTNT) will be secondary endpoints.
- To compare selected outcomes from the external comparator cohort to those from the Zuma- 5 clinical trial.
- To describe patient's quality of life based on available patient reported outcomes (PROs) as an exploratory objective.

Main inclusion criteria

- Patients aged ≥18 years
- Patients with histologically confirmed diagnosis of iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal / extranodal based on criteria established by the World Health Organization (WHO) 2016 classification (restricted to patients with FL in the analysis stage)
- Patients with r/r disease (i.e., r/r iNHL) starting third or higher line of therapy on or after 23rd July 2014 (exact date differed according to individual cohort component protocols)

Main Exclusion criteria

- Transformed FL
- FL Histological Grade 3b
- Prior anti-CD19 CAR T-cell therapy or other genetically modified T-cell therapy
- Eligible within 12 months before of the end of the study database cut-off

Trial conduct

- In total, 82 patients were included in the overall SCHOLAR-5 cohort, which comprised the following subcohorts:
- Subcohort A (IQVIA): 56 patients and 78 eligible lines of therapy

- Subcohort B (Vanderbilt): 2 patients and 4 eligible lines of therapy
- Subcohort C (DELTA): 24 patients and 24 eligible lines of therapy
- From the 86 patients ZUMA-5 follow-up 1 IAS cohort, the 60 patients who had received ≥3 prior lines of therapy were the focus of this report.

Results

Comparative analyses are provided in the following tables:

Table 12: Number of patients available for analysis from each study

Analysis	SCHOLAR-5				ZUMA-5
	IQVIA	Vanderbilt	DELTA	Total SCHOLAR-5	
≥3 prior lines of therapy					
Primary comparative analysis	56	2	24	82	60
Excluding patients from DELTA	56	2	0	58	60
Modified effectiveness analysis set (mEAS)	42	2	23	67	60
Analysis without multiple imputation	55	2	24	81	60
ZUMA-5 Safety analysis set	56	2	24	82	78
Patients with positive POD24 status	17	0	0	17	34
Patients refractory at index date	43	2	24	69	48
Patients with prior SCT	15	0	4	19	16

Note: In the primary comparative analysis, the ZUMA-5 is from the Inferential Analysis set, whereas the Safety Analysis Set is used to obtained data when not restricted to 18 months of follow-up. POD24: progressed disease within 24 months after initiation of first line anti-CD20 chemo combination therapy.

Table 13: Propensity score variables, prior to weighting (≥3 prior lines of therapy)

		SCHOLAR-5	ZUMA-5	p-value	SMD
Number of patients		82	60		
POD24	Yes	29 (35.4%)	34 (56.7%)	0.014	0.437
	No	53 (64.6%)	26 (43.3%)		
	Missing	0 (0%)	0 (0%)		
Prior lines of therapy	Mean	3.72	4.30	0.009	0.446
	SD	1.20	1.39		
	Median	3.00	4.00		
	Q1	3.00	3.00		
	Q3	4.00	5.00		
	Min	3.00	3.00		

	Max	8.00	9.00		
	N	82	60		
	Missing	0	0		
Relapsed/refractory to prior line of therapy	Relapsed	16 (19.5%)	12 (20.0%)	0.943	0.012
	Refractory	66 (80.5%)	48 (80.0%)		
	Missing	0 (0%)	0 (0%)		
Prior SCT	Yes	21 (25.6%)	16 (26.7%)	0.888	0.024
	No	61 (74.4%)	44 (73.3%)		
	Missing	0 (0%)	0 (0%)		
Tumor bulk 7cm or greater	Yes	16 (19.4%)	14 (23.3%)	0.589	0.097
	No	66 (80.6%)	46 (76.7%)		
	Missing	0 (0%)	0 (0%)		
Time since last treatment (months)	Mean	11.94	7.54	0.222	0.220
	SD	26.12	10.90		
	Median	2.02	2.94		
	Q1	0.75	1.63		
	Q3	10.63	6.53		
	Min	0	0		
	Max	172.93	51.06		
	N	82	60		
	Missing	0	0		
Complete or partial response to prior line of therapy	Yes	44 (53.7%)	24 (40.2%)	0.130	0.273
	No	38 (46.3%)	36 (59.8%)		
	Missing	0 (0%)	0 (0%)		
Age 65+	Yes	42 (51.2%)	21 (35.0%)	0.058	0.332
	No	40 (48.8%)	39 (65.0%)		
	Missing	0 (0%)	0 (0%)		
Prior anti-CD20 + alkylator combination treatment	Yes	74 (90.2%)	60 (100%)	0.673	0.465
	No	8 (9.8%)	0 (0%)		
	Missing	0 (0%)	0 (0%)		

The response rates (ORR and CR) in ZUMA-5 after propensity score weighing were higher than in SCHOLAR-5, which can be seen in Table 15.

Table 14: Response rates for ZUMA-5 versus SCHOLAR-5 after propensity score weighting (≥3 prior lines of therapy, primary comparative analysis)

		SCHOLAR-5 (n=59)	ZUMA-5 (n=60)	Odds Ratio (95% CI)	p-value
Objective response	Yes	24 (40.3%)	57 (95.0%)	28.13 (7.37, 107.30)	<0.001
	No	35 (59.7%)	3 (5.0%)		
Complete response	Yes	12 (20.6%)	48 (80.0%)	15.42 (5.83, 40.84)	<0.001
	No	47 (79.4%)	12 (20.0%)		
Partial response	Yes	12 (19.7%)	9 (15.0%)	0.72 (0.26, 2.00)	0.525
	No	48 (80.3%)	51 (85.0%)		
Stable disease	Yes	7 (11.6%)	1 (1.7%)	0.13 (0.01, 1.24)	0.076
	No	52 (88.4%)	59 (98.3%)		

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Initially, the ZUMA-5 trial was designed as a single-arm open-label phase 2 multicenter trial in subjects with r/r iNHL, and initially patients with biopsy proven progression of r/r follicular lymphoma Grade 1, Grade 2 or Grade 3a have been enrolled. Between the original trial protocol, dated 26 November 2016 and the current valid version of amendment 5, dated 24 July 2019, a couple of important changes have been introduced, including the addition of patients with r/r marginal zone lymphoma. According to the final protocol, the two cohorts (FL and MZL) were analysed together with very different follow up criteria. The minimum follow-up for MZL patients for the primary analysis was 4 weeks, while the minimum follow-up for FL patients was 12 months. As the sought indication is only for FL pooling of MZL and FL patients is not considered sensible.

The trial was a single-arm open-label trial, and therefore sensitive to selection bias and assessment bias. A DSMB was tasked with the interim review of data. The Applicant further planned to protect the conduct of study via limited access of company members to the data of the ongoing trial which was defined in a "Trial Integrity Document". However, the document showed that many subjects had broad access to raw and aggregated data at all times. No firewall was in place. Functions such as biostatisticians were granted full access to the data at any time and were involved in drafting protocol amendments which included substantial changes to the confirmatory analyses (including changes in endpoints, analysis populations, number and timing of interim analyses and type 1 error control over interim analyses). Interim analyses 4 and 5 were furthermore defined only after the successful interim analysis 3 was conducted. This shows that the conduct of trial was not to the usual standards for a well conducted confirmatory trial, but is not expected to have a major negative impact on general data integrity.

The high number of relevant changes and adaptations of the study protocol (6 protocol amendments) and the SAP during the conduct of the trial is noticeable, and may result from the clinical trial initially not having been planned as a pivotal and/or supportive clinical trial for the indication extension on r/r FL. However, no major impact on the data is estimated. The change to add prior therapy with an anti-CD20 monoclonal antibody combined with an alkylating agent as inclusion criterion, e.g., was required in order to ensure that subjects have received standard first line therapy prior to enrollment.

As requested, the Applicant provided data on clinical efficacy of axicabtagene ciloleucel in the indication of r/r FL after 3 or more prior lines of therapy, excluding subjects with centrally confirmed non-FL and for a recent data cutoff date (24-month follow-up analysis data cutoff date: 31 March 2021). The originally reported results for ORR, CR and duration of response in subjects treated with axicabtagene ciloleucel after 3L+ therapy remain compelling, although uncertainties related to a single arm trial may be raised. Most of the included patients had not received prior HDT and autologous ASCT. Due to the safety and the logistic issues of CAR-T therapy, this treatment should be reserved to FL grade 1-3a patients following at least 3-4 prior therapies, including HDT. Patients with FL Grade 3B have been excluded from the pivotal trial, while the proposed target indication in r/r FL actually includes all grade FL, including FL Grade 3B. The extrapolation to patients with FL Grade 3B is considered permissible, as in clinical practice FL Grade 3B is often treated as DLBCL, for which axi-cel is also indicated.

A relatively large proportion of subjects (n=23; 19%) reported an important protocol deviation (IPD), from which only a minority [n = 3;2 %)] could be explained as related to the outbreak of the COVID-19 pandemic. Most of the IPDs related to missing data were missed FU-antibody samples, missed two

consecutive exams and missed post treatment PET-CT and/or diagnostic CTs. Moreover, there were important differences in number and nature of protocol deviations between study sites, requiring the Applicant's remote observation of one site, were n=111 PDs occurred in 7 subjects included. However, no major risks were identified and it was concluded that these IPD may not had a negative impact on general data integrity.

Bridging therapy between leukapheresis and LDC based on investigator decision was not excluded according to the ZUMA-5 clinical trial protocol and 4 subjects with FL excluding centrally confirmed non-FL received bridging therapy. For subjects who received bridging chemotherapy, PET-CT scan was to be performed to establish a new baseline before the start of the lymphodepleting chemotherapy, which ensured that bridging chemotherapy did not impact the analysis of the disease response.

Efficacy data and additional analyses (based on 24-month DCO)

ZUMA-5

The full analysis set (FAS) of subjects with FL excluding subjects with centrally confirmed non-FL and who received ≥ 3 lines of prior therapy, which is the claimed target indication of this MAA, comprised 75 subjects. The majority of subjects presented with disease stage Grade III (n=34; 45%) and Grade IV (n=31; 41%), and with intermediate (FLIPI total score of 2) (n=30; 40%) and high risk (FLIPI total score of 3-5) (n=34; 45%) disease. The retrospective CD19 status for n=69/75 evaluable subjects per central assessment revealed that 56 subjects of these 69 (90.3%) were confirmed CD19 positive, 6 subjects were CD19 negative, and 7 subjects' CD19 antigen status were missing/inconclusive at baseline. The median number of prior therapy lines was 4 (range: 3 to 10), and 45 subjects (60%) had received 4 or more lines of therapy. Twenty two subjects (29%) had previously received auto-SCT and 30 subjects (40%) had previously been treated with a PI3K inhibitor. With 91% of subjects with at least 1 high-risk prognostic factor (progression within 24 months from the first anti-CD20-chemotherapy combination therapy, within 6 months after the last line of prior therapy, or after auto-SCT), overall this population can been considered at high risk with a medical need for alternative treatment options.

Response rates at 24 months follow-up in the FAS for subjects with FL who received ≥ 3 lines of prior therapy, excluding subjects with centrally confirmed non-FL (n = 75): the primary and secondary endpoints ORR and CR were 91% (68 of 75 subjects, 95% CI: 82%, 96%) and 77% (58 of 75 subjects, 95% CI: 66%, 86%).

With regard to DOR the KM-median was 38.6 months (95% CI: 24.7, NE) in the FAS for subjects with FL who received ≥ 3 lines of prior therapy, excluding subjects with centrally confirmed non-FL. The subjects with FL had a median follow-up time for DOR of 22.6 months (95% CI: 18.8, 23.0 months). Among the 75 subjects with FL who received ≥ 3 lines of prior therapy, KM estimates of PFS rates at 24 months was 71.8% (95% CI: 58.6%, 81.4%). The KM median for PFS was 40.2 months (95% CI: 26.6, NE). The KM median for OS was not reached (95% CI: 40.2 months, NE), with a median follow-up time of 29.7 months (95% CI: 26.9, 31.87 months). Estimates of OS at 24 months was 85.5% (95% CI: 74.6, 91.9%).

With regard to analyses for DOR and PFS, patients who received other anticancer therapies (including HSCT and axi-cel retreatment) were censored. As this kind of analysis might be prone to informative censoring, upon request, sensitivity analyses for DOR and PFS in the FL FAS excluding centrally confirmed non-FL who received ≥ 3 prior lines of therapy, considering the start of other new anticancer therapies or axi-cel retreatment in the absence of prior documented progression as an event (EMA censoring rules), were provided. Although a larger difference in median PFS has been noted between primary and sensitivity analysis (40.2 months and 28.9 months, respectively), outcomes for DOR were very similar (both median and K-M plots) and K-M curves for PFS also followed a similar pattern. In conclusion, censoring patients

who started a new anticancer therapies or were retreated with axi-cel retreatment in the absence of prior documented progression as reported by central assessment on DOR and PFS outcomes, is not considered impactful for the interpretation of data. Median follow-up time for TTNT was 29.3 months (95% CI: 25.7, 33.6 months). The KM median TTNT was 40.2 months (95% CI: 26.6, NE). The longest TTNT was 43.3 months as of the data cutoff date. The KM estimates of the proportion of subjects who had not commenced subsequent therapy at Months 24 was 67.0% (95% CI: 54.8%, 76.6%).

Although the number of subjects with CD19 negative status at baseline is small, and thus results should be interpreted with caution, efficacy outcomes (CR rate, ORR and DOR) and PK in patients with baseline $CD19^-$ status seemed to be at least non-inferior compared to the efficacy outcomes and PK in patients with $CD19^+$ status. In addition, although the data on confirmed CD19 antigen status at relapse are few, there is no evidence of $CD19^-$ escape.

Only n=8/75 subjects (11%) in FAS with FL excluding subjects with centrally confirmed non-FL and who received ≥ 3 lines of prior therapy were non-US subjects (in particular from France), which might compromise the external validity of the ZUMA-5 study. A significant difference observed is the higher number of prior auto-SCT (65%/EU versus 25%/US). However, response (CR rate) and safety profile seem consistent between subjects from EU and US.

The results provided for the requested revised analysis sets, and for the 24-month data cut-off date indicate that the ORR and CR rate of subjects with FL who received 3 or more lines of therapy in the FAS and IAS excluding centrally confirmed non-FL were similar (ORR: 91% versus 95% respectively; CR rate: 77% versus 78%, respectively). The KM median estimates of DOR, PFS, OS, and TTNT in the FAS and IAS were similar (DOR: 38.6 months in each analysis set; PFS: 40.2 versus 28.0 months, respectively; OS: not estimable in each analysis set; TTNT: 40.2 versus 39.6 months, respectively).

SCHOLAR-5

SCHOLAR-5 as a synthetic supportive trial can be acknowledged in general. In a comparative analysis ORR and CR in SCHOLAR-5 was lower than in ZUMA-5. The statistical challenges such as potential bias (due to different sources) which are inherent to single-arm trials with external controls make further conclusions from this data impossible. OS and PFS from single-arm trials should not be compared with external controls due to an unknown magnitude of bias. The data from SCHOLAR-5 overall is considered overall supportive.

2.5.3. Conclusions on the clinical efficacy

The data presented on primary and secondary endpoints in subjects with r/r FL, the target indication in the ZUMA-5 trial, indicate a benefit for the patients. The trial was a single-arm open label trial without a good firewall in place to protect decision making to be influenced by the available data. Decisions to include further interim analyses (IA4 and 5) were even made post hoc after the results from interim analysis 3 were known. Given that the first efficacy interim analysis (IA3) was significant and given the very high effects both for ORR as well as CRR at all analyses this is not considered of major relevance for the overall extension of indication procedure. The trial is considered to have met the primary objective at IA3, which is then numerically supported by analyses with more subjects and longer follow up. The conduct of trial was not up to the usual standards, however, this is not expected to have a negative impact on general data integrity.

2.6. Clinical safety

Introduction

The important identified risks and the potential risks identified for axicabtagene ciloleucel are similar to the AEs identified for this product class. No further risks and AEs could be identified which would be specific for axicabtagene ciloleucel or for the indications to be treated with axicabtagene ciloleucel. The important identified risks are CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia.

A new indication is being sought for the treatment of adult patients with r/r FL after three or more lines of systemic therapy with this submission. The evaluation of safety is based on the ZUMA-5 study. The initial analysis cutoff date is March 12, 2020, which represents the 12 months follow-up data. Additional safety data were from the follow-up analysis 1, with a data cutoff date of 14 September 2020, (hereafter referred to as the 18-month analysis) of ZUMA-5. This prespecified analysis was performed when at least 80 subjects with FL had had the opportunity to be followed for 18 months after axicabtagene ciloleucel infusion.

Supporting safety data are also presented from 3 studies of axicabtagene ciloleucel in subjects with aggressive large B-cell lymphomas: KTE-C19-101 (ZUMA-1), KTE-C19-109 (ZUMA-9), and KTE-C19-112 (ZUMA-12). The additional safety data are provided with a data cutoff date of 11 August 2020.

Patient exposure

Throughout the documents, the Applicant presented data for patients with FL, but also for patients with Marginal Zone Lymphoma (MZL), sometimes combining these patients in an indolent NHL group. For the primary safety evaluation in this AR, the data obtained in FL patients were considered as main data (18-month follow-up, data cutoff 14 September 2020), and data from MZL patients were considered supportive.

The safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel.

Table 15. Analysis sets (data cutoff 14 Sept 2020)

	Follicular Lymphoma (N=127)	Marginal Zone Lymphoma (N=25)	Overall[a] (N=153)
Full analysis set, n (%)	127 (100)	25 (100)	153 (100)
Subjects with 3 or more lines of prior therapy, n (%)	80 (63)	16 (64)	97 (63)
Safety analysis set, n (%)	124 (98)	24 (96)	148 (97)
Subjects with 3 or more lines of prior therapy, n (%)	78 (61)	16 (64)	94 (61)
Inferential analysis set, n (%)	86 (68)	23 (92)	109 (71)
Subjects with 3 or more lines of prior therapy, n (%)	60 (47)	16 (64)	76 (50)
Safety retreatment analysis set, n (%)	11 (9)	2 (8)	13 (8)

Data cutoff date: 14Sep2020.
Note: There are 181 subjects screened and 153 enrolled.
The full analysis set consists of all enrolled subjects.
The safety analysis set is defined as all subjects treated with any dose of axicabtagene ciloleucel.
The inferential analysis set consists of the first 86 subjects with follicular lymphoma enrolled (and who meet the eligibility criteria for the pivotal cohort), treated with any dose of axicabtagene ciloleucel, and had opportunity to be followed for 18 months from the axicabtagene ciloleucel infusion.
The safety retreatment analysis set consists of all subjects who underwent retreatment with axicabtagene ciloleucel.
a. One subject was found to have disease type diffuse large B-cell lymphoma after enrollment, did not receive axicabtagene ciloleucel infusion, and then discontinued the study. This subject is only included in the Overall column.

In total, as of the 18-month follow-up (cutoff 14 September 2020), 153 subjects with iNHL were enrolled (ie, underwent leukapheresis): **127 subjects with FL**, 25 subjects with MZL, and 1 subject with DLBCL. The DLBCL was discovered via a pretreatment biopsy that was examined after the subject enrolled;

consequently, the subject was deemed ineligible and was withdrawn from the study. A total of 148 subjects (**124 subjects with FL** and 24 subjects with MZL) had received lymphodepleting chemotherapy and axicabtagene ciloleucel; 5 subjects had not received lymphodepleting chemotherapy or axicabtagene ciloleucel. One of these 5 subjects was the aforementioned subject with DLBCL who was deemed ineligible; the reasons for not receiving lymphodepleting chemotherapy or axicabtagene ciloleucel for the other 4 subjects were as follows:

- One subject with FL died due to cardiac arrest before having the opportunity to be treated on study.

- One subject with FL was found to be ineligible after enrollment but prior to treatment due to inadequate platelet levels (< 75,000 per mm3); this subject was treated under a compassionate use protocol and was not included in the safety analysis set.

- One subject with FL was leukapheresed, but experienced a CR prior to lymphodepleting chemotherapy and had partially withdrawn at the time of data cutoff; the subject remains in follow-up.

- One subject with MZL was leukapheresed, but experienced a CR prior to lymphodepleting chemotherapy and was considered ineligible to receive infusion based on inclusion criteria; the subject remains in follow-up.

Six subjects with FL received bridging therapy between enrollment and lymphodepleting chemotherapy. New baseline scans were obtained after bridging treatment and before lymphodepleting chemotherapy.

Thirteen subjects (11 subjects with FL and 2 subjects with MZL) were retreated with axicabtagene ciloleucel. These subjects are included in the retreatment analysis set. The outcome of retreatment for these subjects is not part of the main inferential analysis and is analysed separately. (For the retreated patients the safety profile was similar to that observed for the main analysis.)

As of the data cutoff date, 18 subjects (14 subjects with FL and 4 subjects with MZL) who received axicabtagene ciloleucel had died. One additional subject with FL who received axicabtagene ciloleucel was removed from the study due to investigator decision and ultimately died.

For the 124 subjects with FL who received axicabtagene ciloleucel, the median actual study follow-up time was 20.34 months (range: 0.3 to 37.7 months); 91 of 127 subjects (73%) had a potential study follow-up time of at least 18 months.

Table 16: Demographics (Safety Analysis Set)

	Follicular Lymphoma (N = 124)
Age (years)	
N	124
Mean (STDEV)	59.0 (9.9)
Median (Q1, Q3)	60.0 (53.0, 67.0)
Min, Max	34, 79

Age category, n (%)	
< 65 Years	86 (69)
>= 65 Years	38 (31)
Sex, n (%)	
Male	73 (59)
Female	51 (41)
Ethnicity, n (%)	
Hispanic or Latino	6 (5)
Not Hispanic or Latino	118 (95)
Missing	0 (0)
Race, n (%)	
Asian	2 (2)
Black or African American	4 (3)
White	115 (93)
Other	3 (2)
Country, n (%)	
United States	114 (92)
France	10 (8)

Data cutoff date: 14Sep2020.

Table 17: Baseline Characteristics (Safety analysis set)

	Follicular Lymphoma (N = 124)
ECOG performance status, n (%)	
0	78 (63)
1	46 (37)
Histologically diagnosed disease type per local lab, n (%)	
Follicular lymphoma	124 (100)
Marginal zone lymphoma	0 (0)
Follicular lymphoma histological category at study entry, n (%)	
Grade 1	33 (27)
Grade 2	61 (49)
Grade 3a	30 (24)
Marginal zone lymphoma histological category, n (%)	
Nodal	-
Extranodal	-
Disease stage, n (%)	
I	5 (4)
II	13 (10)
III	45 (36)
IV	61 (49)
FLIPI total score, n (%)	
0	4 (3)
1	18 (15)
2	48 (39)
3	35 (28)
4	16 (13)
5	3 (2)
Low risk (0 - 1)	22 (18)
Intermediate risk (2)	48 (39)
High risk (3 - 5)	54 (44)

Relapsed/refractory subgroup[a], n (%)	
Relapsed	40 (32)
Refractory	84 (68)
Double refractory subgroup[a], n (%)	
Yes	36 (29)
No	88 (71)
Number of prior lines of therapy[b], n (%)	
1[c]	3 (2)
2	42 (34)
3	32 (26)
4	25 (20)
≥ 5	21 (17)
N	123
Mean (STDEV)	3.34 (1.59)
Median (Q1, Q3)	3.00 (2.00, 4.00)
Min, Max	1.0, 10.0
Response to last line of therapy, n (%)	
Complete response	34 (27)
Partial response	24 (19)
Stable disease	25 (20)
Progressive disease	23 (19)
Not evaluable	4 (3)
Unknown	13 (10)
Receiving prior autologous stem cell transplant, n (%)	
Yes	30 (24)
No	94 (76)
Time to relapse from first anti-CD20-chemotherapy combination therapy[d], n (%)	123
≥ 24 months	40 (33)
< 24 months	68 (55)
High tumor bulk as defined by GELF criteria[e], n (%)	64 (52)

Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm	32 (26)
Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm	22 (18)
Presence of B symptoms	8 (6)
Splenomegaly	22 (18)
Pleural effusions or peritoneal ascites	5 (4)
Cytopenias	15 (12)
Leukemia	1 (1)
Prior PI3K inhibitor, n (%)	
Yes	34 (27)
No	90 (73)
Prior anti-CD20 single agent[f], n (%)	
Yes	39 (31)
No	85 (69)
Prior alkylating single agent, n (%)	
Yes	16 (13)
No	108 (87)
Prior anti-CD20 + alkylating agent, n (%)	
Yes	123 (99)
No[g]	1 (1)
Prior lenalidomide, n (%)	
Yes	38 (31)
No	86 (69)
Bone marrow assessment at baseline[h], n (%)	
Lymphoma present	33 (27)
Lymphoma present but not FL/MZL[g]	1 (1)
Lymphoma not present	89 (72)
Unknown	1 (1)

Data cutoff date: 14Sep2020.

a. Subjects with iNHL who progressed within 6 months of completion of the most recent prior treatment are defined as refractory. Subjects with iNHL who progressed > 6 months from completion of the most recent prior treatment are defined as relapsed. Subjects with iNHL who progressed within 6 months of completion each of the first 2 lines of prior treatment are defined as double refractory.
b. One subject received prior therapy that was given for DLBCL, not for the primary disease of FL.
c. Subjects were enrolled before the implementation of Protocol Amendment 2, which required subjects to have had at least 2 prior lines of therapy.
d. Time to relapse is defined as the time from initiation of the first line anti-CD20-chemotherapy combination therapy to progression. The number of subjects with time to relapse is based on those who had progressed with date of progression. Percentages are based on the number of subjects who ever received anti-CD20-chemotherapy combination therapy.
e. Disease burden, as defined by any of GELF criteria (subjects who meet the criteria for high tumor bulk versus subjects who do not meet the criteria for high tumor bulk): Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm, Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm, B symptoms, splenomegaly, pleural effusions or peritoneal ascites, cytopenias, or leukemia.
f. Prior anti-CD20 single agent includes rituximab, ofatumumab, or obinutuzumab.
g. One subject did not have documentation to support that prior lines of therapy were administered for FL. The date of FL diagnosis was entered approximately 2 weeks prior to screening. Due to the lack of documentation to support a FL diagnosis at the time any of the therapies were administered, the site was asked to remove all lines of therapy. The absence of documentation to support an FL diagnosis when prior therapies were administered is considered an important protocol deviation. This subject is not included in the inferential analysis set. One subject with MZL did not receive anti-CD20 therapy due to the disease being previously documented as CD20 negative. This subject is included in the inferential analysis set.
h. Bone marrow assessment at baseline for lymphoma presence is based on investigator reported Lugano bone marrow assessment/ bone marrow assessment using aspirate or core biopsy at screening. If these are not available, lymphoma presence is based on diagnosis history of bone marrow involvement.

Exposure to LD

All subjects in the ZUMA-5 safety analysis set received the planned total BSA-adjusted dose of cyclophosphamide (1500 mg/m^2) and fludarabine (90 mg/m^2).

Exposure to Axicabtagene Ciloleucel

Among subjects with FL, the median weight-adjusted dose of axicabtagene ciloleucel was 2.0 x 10^6 anti-CD19 CAR T cells/kg (range: 1.3 x 10^6 to 2.1 x 10^6 cells/kg). The median total number of anti-CD19 CAR T cells in the axicabtagene ciloleucel infusion was 170.0 x 10^6 cells (range: 100.0 x 10^6 to 200.0 x 10^6 cells), and the median total number of T cells infused was 283.70 x 10^6 cells (range: 123.5 x 10^6 to 769.2 x 10^6 cells). The majority of subjects (120 subjects, 97%) received within 10% of the planned total dose.

The median duration for hospitalization after the axicabtagene ciloleucel infusion was 13.0 days (range: 8.0 to 40 days) for subjects with FL. The median duration in the intensive care unit was 6 days for subjects with FL (range: 2 to 24 days).

Adverse events

The overall summary of AEs at the 18 months cutoff is displayed in Table 19.

As of the data cutoff date, 3 subjects with FL (2%) who received axicabtagene ciloleucel had died due to AEs:

- 1 subject died due multiple organ dysfunction syndrome on Day 7 that was secondary to CRS (the death was deemed related to axicabtagene ciloleucel),

- 1 subject died due to cardiopulmonary arrest that followed an aortic dissection on Day 399 (the death was deemed unrelated to axicabtagene ciloleucel),

- 1 subject died due to disease progression on Day 47 that was categorized as an AE (Grade 5 B-cell lymphoma) because it occurred within the 3-month AE reporting window.

Overall, safety results were generally similar in the subset of subjects who had 3 or more lines of prior therapy (99% subjects with TEAE, 47% with SAEs, 79% with CRS, and 55% with neurologic events) compared with those found for the larger safety analysis set in subjects with 2 or more lines of prior therapy.

Table 18: Overall Summary of AEs (data cutoff 14 Sept 2020)

	Follicular Lymphoma (N = 124) n (%)
Any TEAE	123 (99)
Worst Grade 5	3 (2)
Worst Grade ≥ 3	105 (85)
Any serious TEAE	57 (46)

	Follicular Lymphoma (N = 124) n (%)
Worst Grade 5	3 (2)
Worst Grade ≥ 3	44 (35)
Any axicabtagene ciloleucel-related TEAE	118 (95)
Worst Grade 5	1 (1)
Worst Grade ≥ 3	71 (57)
Any serious axicabtagene ciloleucel-related TEAE	38 (31)
Worst Grade 5	1 (1)
Worst Grade ≥ 3	26 (21)
Any TE neurologic event	70 (56)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	19 (15)
Any serious TE neurologic event	19 (15)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	14 (11)
Any TE CRS	97 (78)
Worst Grade 5	1 (1)
Worst Grade ≥ 3	8 (6)
Any serious TE CRS	15 (12)
Worst Grade 5	1 (1)
Worst Grade ≥ 3	8 (6)
Any TE hypogammaglobulinemia	24 (19)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	1 (1)
Any TE cytopenias	91 (73)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	86 (69)
Any TE infections	64 (52)
Worst Grade 5	0 (0)
Worst Grade ≥ 3	19 (15)
Any TE tumor lysis syndrome	0 (0)
Any TE graft-versus-host-disease	0 (0)

Data cutoff date: 14Sep2020.

Among subjects with FL, the most common AEs by preferred terms were pyrexia (103 subjects, 83%), hypotension (59 subjects, 48%), and headache (55 subjects, 44%). The most common AEs (>60% of subjects) by SOC were general disorders and administration site conditions (113 subjects, 91%), nervous system disorders (90 subjects, 73%), and gastrointestinal disorders (88 subjects, 71%).

Twenty-nine subjects (23%) had worst Grade 3 AEs, 73 subjects (59%) had worst Grade 4 AEs, and 3 subjects (2%) had worst Grade 5 AEs. The most common worst Grade 3 or higher AEs were neutropenia (44 subjects, 35%), and neutrophil count decreased and anemia (29 subjects each, 23%).

Serious adverse event/deaths/other significant events

SAEs

Among subjects with FL, 57 subjects (46%) had at least 1 SAE, the most frequently reported of which were pyrexia (16 subjects, 13%), encephalopathy (8 subjects, 6%), pneumonia (8 subjects, 6%), and confusional state (7 subjects, 6%). The most common worst Grade 3 or higher SAEs were encephalopathy (8 subjects, 6%), pneumonia (7 subjects, 6%), and confusional state (4 subjects, 3%).

Deaths

Among all subjects who received axicabtagene ciloleucel, 15 FL subjects had died as of the data cutoff date (14 September 2020), including 2 which occurred within 3 months of axicabtagene ciloleucel infusion, and 13 occurred > 3 months after the infusion):

- Nine subjects from progressive disease (including one subject with ≥3 lines of prior therapy who died due to PD on Day 47 that was reported as Grade 5 B-cell lymphoma because it occurred within the AE reporting window)

- Two subjects from AE (both in subjects with ≥3 lines of prior therapy): One subject died on Day 7 due to multiple organ dysfunction syndrome that was secondary to CRS, both of which were attributed to the axicabtagene ciloleucel infusion. One subject died on Day 399 due to cardiopulmonary arrest that followed an aortic dissection; the subject remained in CR at Month 12 (the last visit before her death) per central assessment. The death was deemed unrelated to axicabtagene ciloleucel.

- One from secondary malignancy: This subject died on Day 337 due to acute myeloid leukemia (not attributable to axicabtagene ciloleucel) after having partially withdrawn consent from the study and having agreed to be followed for survival.

- One from infection (who died after partial withdrawal of consent) (in subject with ≥3 lines of prior therapy): The subject died on Day 715 due to an infection (coccidioidomycosis) that was not attributable to axicabtagene ciloleucel. The subject was in CR at Month 18 (the last visit before his death) per central assessment.

- Two from unknown causes: One subject died due to unknown reasons on Day 692; this subject had been removed from the study by the investigator. The investigator discovered the death in public records without any details. One additional subject died due to unknown reasons on Day 697.

Table 19: Summary of Deaths, Including Cause of Deaths (Safety Analysis Set, 14 Sep 2020 cutoff)

	Follicular Lymphoma (N = 124) n (%)
Subjects who died	15 (12)
Deaths that occurred <= 30 days of axicabtagene ciloleucel infusion	1 (1)
Deaths that occurred > 30 days through 3 months (92 days) of axicabtagene ciloleucel infusion	1 (1)
Deaths that occurred > 3 months (92 days) after axicabtagene ciloleucel infusion	13 (10)
Primary cause of death	15 (12)
AE due to reasons other than PD or subsequent therapy	2 (2)
Progressive disease[a]	9 (7)
Secondary malignancy	1 (1)
Other, infection[b]	1 (1)
Other, unknown	1 (1)
Other, unknown, found via public record	1 (1)

Data cutoff date: 14Sep2020.

AEs of Special Interest

Important identified risks

1. CRS

CRS was graded as a syndrome according to a modification of the criteria established by Lee and Colleagues. All cases of CRS were considered related to axicabtagene ciloleucel.

Table 20: Subject Incidence of CRS and CRS Symptoms Occurring in ≥ 4% of Subjects Overall (Safety Analysis Set)

MedDRA Preferred Term Worst CTCAE Grade	Follicular Lymphoma (N = 124) n (%)
Subjects with any TE CRS[a]	97 (78)
Grade 5	1 (1)
Grade ≥3	8 (6)
CRS symptoms by preferred term[b]	
Pyrexia	94 (97)
Grade 5	0 (0)
Grade ≥3	6 (6)
Hypotension	39 (40)
Grade 5	0 (0)
Grade ≥3	3 (3)
Chills	25 (26)
Grade 5	0 (0)
Grade ≥3	0 (0)
Hypoxia	23 (24)
Grade 5	0 (0)
Grade ≥3	6 (6)
Sinus Tachycardia	25 (26)
Grade 5	0 (0)
Grade ≥3	2 (2)
Headache	19 (20)
Grade 5	0 (0)

Grade ≥3	0 (0)
Tachycardia	9 (9)
Grade 5	0 (0)
Grade ≥3	0 (0)
Nausea	7 (7)
Grade 5	0 (0)
Grade ≥3	0 (0)
Vomiting	7 (7)
Grade 5	0 (0)
Grade ≥3	0 (0)
Fatigue	6 (6)
Grade 5	0 (0)
Grade ≥3	0 (0)
Malaise	6 (6)
Grade 5	0 (0)
Grade ≥3	0 (0)
Alanine Aminotransferase Increased	4 (4)
Grade 5	0 (0)
Grade ≥3	2 (2)
Myalgia	5 (5)
Grade 5	0 (0)
Grade ≥3	0 (0)

Data cutoff date: 14Sep2020.

The median time to onset was 4 days (range: 1 to 15 days) for subjects with FL. As of the data cutoff date, CRS had resolved in all but 1 subject in ZUMA-5; the subject with unresolved CRS had FL and died on Day 7 due to multiple organ dysfunction syndrome that was secondary to CRS. For the 96 subjects with FL whose CRS had resolved, the median duration of CRS was 6 days (range: 1 to 27 days).

Table 21: Concomitant medications of interest (Safety Analysis Set)

	Follicular Lymphoma (N = 124) n (%)
Subjects with any concomitant medications of interest	79 (64)
Steroids	
Any	50 (40)
Used for treatment of CRS	19 (15)
Used for treatment of NE	38 (31)
Other AEs	12 (10)
Tocilizumab	
Any	56 (45)
Used for treatment of CRS	56 (45)
Used for treatment of NE	7 (6)
Other AEs	5 (4)
Steroid or tocilizumab	
Any	68 (55)
Steroid and tocilizumab	
Any	38 (31)
Vasopressors	
Any	15 (12)
Used for treatment of CRS	7 (6)
Used for treatment of NE[a]	1 (1)
Nonsteroidal immunosuppressive agents	
Any	1 (1)
Used for treatment of CRS	1 (1)
Used for treatment of NE	0 (0)
Immunoglobulins	
Any	34 (27)

Data cutoff date: 14Sep2020.

2. Neurologic events

Table 22: Subject Incidence of Neurologic Events (Safety Analysis Set)

MedDRA Preferred Term Worst CTCAE Grade	Follicular Lymphoma (N = 124) n (%)
Subjects with any TE neurologic event	70 (56)
Grade 5	0 (0)
Grade ≥3	19 (15)
Tremor	36 (29)
Grade 5	0 (0)
Grade ≥3	1 (1)
Confusional State	28 (23)
Grade 5	0 (0)
Grade ≥3	6 (5)
Encephalopathy	24 (19)
Grade 5	0 (0)
Grade ≥3	10 (8)
Aphasia	16 (13)
Grade 5	0 (0)
Grade ≥3	3 (2)
Somnolence	9 (7)
Grade 5	0 (0)
Grade ≥3	2 (2)
Agitation	10 (8)
Grade 5	0 (0)
Grade ≥3	2 (2)
Disturbance In Attention	7 (6)
Grade 5	0 (0)
Grade ≥3	0 (0)
Dysarthria	6 (5)
Grade 5	0 (0)
Grade ≥3	1 (1)

Paraesthesia	6 (5)
Grade 5	0 (0)
Grade ≥3	0 (0)
Delirium	3 (2)
Grade 5	0 (0)
Grade ≥3	2 (2)
Hallucination	6 (5)
Grade 5	0 (0)
Grade ≥3	2 (2)
Memory Impairment	4 (3)
Grade 5	0 (0)
Grade ≥3	0 (0)
Amnesia	2 (2)
Grade 5	0 (0)
Grade ≥3	0 (0)
Dysgraphia	3 (2)
Grade 5	0 (0)
Grade ≥3	0 (0)
Seizure	2 (2)
Grade 5	0 (0)
Grade ≥3	0 (0)
Apraxia	1 (1)
Grade 5	0 (0)
Grade ≥3	0 (0)
Ataxia	1 (1)
Grade 5	0 (0)
Grade ≥3	0 (0)
Cognitive Disorder	1 (1)
Grade 5	0 (0)
Grade ≥3	0 (0)
Hypoaesthesia	2 (2)
Grade 5	0 (0)
Grade ≥3	0 (0)
Immune Effector Cell-Associated Neurotoxicity Syndrome	2 (2)
Grade 5	0 (0)
Grade ≥3	1 (1)

Data cutoff date: 14Sep2020.

For subjects with FL, the median time to event onset was 7 days (range: 1 to 177 days). Six subjects with FL had neurologic events with an onset > 80 days after the axicabtagene ciloleucel infusion; these events were as follows:

- One subject had worst Grade 1 disturbance in attention (which started on Day 94 and was unresolved as of the data cutoff date) and somnolence (Day 200 through Day 219). Only the disturbance in attention was deemed related to axicabtagene ciloleucel.
- One subject had a worst Grade 1 tremor (Day 94 through Day 262) that was deemed related to axicabtagene ciloleucel.

- One subject had worst Grade 1 aphasia (Day 97 through Day 193) that was deemed unrelated to axicabtagene ciloleucel.
- One subject had worst Grade 2 events of amnesia (Day 119 through Day 137) and confusional state (Day 124 through Day 133), neither of which were deemed related to axicabtagene ciloleucel.
- One subject had a worst Grade 1 memory impairment (Day 176 through Day 267) that was deemed unrelated to axicabtagene ciloleucel.
- One subject had a worst Grade 1 hypoaesthesia (Day 452 through Day 456) that was deemed unrelated to axicabtagene ciloleucel.

As of the data cutoff date Sept 2020, three subjects had unresolved neurologic events at the data cutoff: memory impairment [started on Day 59], paresthesia [started on Day 66], and the aforementioned subject with disturbance in attention [started on Day 94]; all Grade 1. These events were all assessed as nonserious and deemed related to axicabtagene ciloleucel. One additional subject with FL had disturbance in attention that was deemed related to axicabtagene ciloleucel (started on Day 94; Grade 1). The subject died due to an unknown cause on Day 692, and the event was recorded to be resolved on the same day.

Among 70 subjects with FL who had neurologic events, 67 subjects (96%) had events that resolved; the events resolved within 3 weeks after the infusion for 41 subjects (59%) and within 8 weeks after the infusion for 54 subjects (77%). Among the 67 subjects with FL whose neurologic events had resolved, the median duration of neurologic events was 14.0 days (range: 1 to 452 days). Three subjects with FL had neurologic events that were present beyond study Day 200 as follows:

- Two subjects had Grade 1 tremor from Day 94 to Day 262 and Day 19 to Day 369, respectively (both events were deemed related to axicabtagene ciloleucel).
- One subject had Grade 1 hypoesthesia from Day 452 to Day 456 that was deemed unrelated to axicabtagene ciloleucel.

There were 11 subjects with FL who had neurologic events that occurred > 30 days but < 200 days after the axicabtgene ciloleucel infusion. All of these neurologic events were Grade 1 except for the events of Grade 2 amnesia and Grade 2 confusional state in 1 FL subject.

3. Cytopenias

Among subjects with FL, 91 subjects (73%) had any cytopenia AEs, and 86 subjects (69%) had worst Grade 3 or higher cytopenia AEs. 79 subjects (64%) had neutropenia AEs of any grade, and 75 subjects (60%) had worst Grade 3 or higher neutropenia AEs. Forty-four subjects (35%) had thrombocytopenia AEs of any grade, and 29 subjects (23%) had worst Grade 3 or higher thrombocytopenia AEs. Forty-four subjects (35%) had anemia AEs of any grade, and 29 subjects (23%) had worst Grade 3 or higher anemia AEs.

The number of subjects with FL who had worst Grade 3 or higher prolonged neutropenia, thrombocytopenia, and anemia AEs (that were present on or after Day 30 following the axicabtagene ciloleucel infusion on Day 0) were 34 subjects (27%), 13 subjects (10%), and 8 subjects (6%), respectively. The duration of cytopenias was calculated for subjects whose events had resolved. The mean (standard deviation) and median (range) times to onset of cytopenias were 16.7 (51.7) and 3.0 (1 to 325) days after axicabtagene ciloleucel infusion, respectively. The median duration of cytopenias were 27.0 (range: 1 to 769) days.

4. Infections

Among subjects with FL, 64 subjects (52%) had infections; 18 subjects (15%) had worst Grade 3 infections and 1 subject (1%) had worst Grade 4 infection. No subject had a worst Grade 5 infection. The most common events by preferred terms within the SOC of infections and infestations were pneumonia (15 subjects, 12%), upper respiratory tract infection (14 subjects, 11%), and oral candidiasis, sinusitis, and urinary tract infection (9 subjects, 7%). The most common bacterial infections were staphylococcal infection (3 subjects, 2%) and clostridium difficile colitis and hemophilus infection (2 subjects each, 2%); all other bacterial infections were reported for 1 subject each (1%). The most common viral infections were influenza (6 subjects, 5%), rhinovirus infection (4 subjects, 3%), and herpes zoster (3 subjects, 2%); all other viral infections were reported for 1 subject each (1%). Opportunistic infections included cytomegalovirus viraemia, mycobacterium kansasii infection, ophthalmic herpes simplex, and systemic candida, all reported in 1 subject each (1%). The most common other types of infections were pneumonia (15 subjects, 12%), upper respiratory tract infections (14 subjects, 11%), and sinusitis and urinary tract infections (9 subjects each, 7%). Worst Grade 3 events included pneumonia (7 subjects, 6%), urinary tract infection (3 subjects, 2%), and staphylococcal infection, clostridium difficile colitis, bacterial infection, Escherichia infection, pneumonia streptococcal, systemic candida, herpes zoster, sinusitis, vascular device infection, bacteremia, kidney infection, prostate infection, and viremia (1 subject each, 1%). The single worst Grade 4 event was sepsis (1 subject, 1%).

5. Hypogammaglobulinemia

Among subjects with FL, 24 subjects (19%) had AEs of hypogammaglobulinemia (17% in of subjects who had 3 or more lines of prior therapy), and the majority were either worst Grade 1 (7 subjects, 6%) or worst Grade 2 (16 subjects, 13%). One subject (1%) had a worst Grade 3 event.

Important potential risks

Secondary Malignancies

All other new malignancies were assessed as being unrelated to axicabtagene ciloleucel.

In the FL patients, there were 9 secondary malignancies identified: squamous cell carcinoma (2 subjects), malignant anorectal neoplasm and secondary anal/rectal cancer (1 subject), and myelodysplastic syndrome (MDS), malignant melanoma, basal cell carcinoma, acute bilineal leukemia, and prostate cancer (1 subject each). In addition, there was 1 subject whose death was flagged as due to secondary malignancy; this subject died due to acute myeloid leukemia after having partially withdrawn consent from the study and having agreed to be followed for survival. The events of acute bilineal leukemia and MDS were deemed related to lymphodepleting chemotherapy.

Immunogenicity

Subjects were tested for immunogenicity. In the FL patients, based on an initial screening assay, 14 subjects were antibody-positive at baseline and 14 of the 123 tested subjects (11%) had a positive antibody test result at any time point. Samples from all 14 subjects were sent for confirmatory testing via a cell-based assay. Results of the confirmatory assay indicated that all 14 subjects were antibody-negative at all time points tested.

Table 23: Anti-Axicabtagene Ciloleucel Antibody Summary (Safety Analysis Set)

	Follicular Lymphoma (N = 124)	Marginal Zone Lymphoma (N = 24)	Overall (N = 148)
Subjects with an on-study result[a], n	123	23	146
Antibody-positive at anytime, n (%)	14 (11)	7 (29)	21 (14)
Subjects with a result at baseline, n	121	23	144
Antibody-positive at baseline, n (%)	14 (11)	6 (25)	20 (14)
Subjects with a post-baseline result, n	121	23	144
Antibody-positive at post-baseline with a negative or no result at baseline, n (%)	3 (2)	1 (4)	4 (3)
Antibody-positive at post-baseline with a negative result at baseline, n (%)	3 (2)	1 (4)	4 (3)
Antibody-positive at post-baseline with no result at baseline, n (%)	0 (0)	0 (0)	0 (0)
Transient[b], n (%)	2 (2)	1 (4)	3 (2)

Data cutoff date: 14Sep2020.
a. Subject is considered on-study on or after enrollment
b. Transient is defined as developing positive post-baseline with a negative or no results at baseline but result at the subject's last timepoint tested within the study period was negative.

Data Source: ADSL, ADIS Program Name: t_antibody.sas Output Generated: 20210405T14:16

RCR

No patient tested positive for RCR.

Tumor Lysis Syndrome

No cases of tumor lysis syndrome were reported.

Aggravation of GVHD

No subject had an aggravation of GVHD that was attributable to axicabtagene ciloleucel.

Arrhythmia

There were 52% FL patients with cardiac arrhythmia AEs (mainly grade 1 or 2). The most common events were sinus tachycardia (33%) and tachycardia (12%). There were 2% of subjects who presented worst Grade 3 cardiac arrhythmias (atrial fibrillation in 1 subject and sinus tachycardia in 2 subjects: all considered related to axicabtagene ciloleucel, not serious). All cardiac arrhythmia events resolved.

Laboratory findings

Among subjects with FL, the most common increased laboratory values were creatinine (79 subjects, 64%), glucose (78 subjects, 63%), and ALT (68 subjects, 55%). The most common worst Grade 3 or higher increased laboratory values were glucose and urate (11 subjects each, 9%), ALT (7 subjects, 6%), and aspartate aminotransferase (AST) and bilirubin (5 subjects each, 4%). The most common decreased laboratory values were leukocytes (122 subjects, 98%), neutrophils (121 subjects, 98%), and hemoglobin (103 subjects, 83%). The most common worst Grade 3 or higher decreased laboratory values were leukocytes (116 subjects, 94%), neutrophils (114 subjects, 92%), and platelets (43 subjects, 35%).

Safety in special populations

1. AEs by Age

Among subjects with FL, compared with subjects who were < 65 years old, subjects who were ≥ 65 years old showed a trend toward a higher incidence of SAEs (42% vs 55%), axicabtagene ciloleucel-related SAEs (27% vs 39%), neurologic events (49% vs 74%), and serious neurologic events (10% vs 26%). In general, subjects ≥ 65 years old had a higher incidence of worst Grade 3 or higher events.

2. AEs by Sex

Among subjects with FL, compared with males, females showed a trend toward a higher incidence of hypogammaglobulinemia (14% vs 27%), worst Grade 3 or higher axicabtagene ciloleucel-related AEs (52% vs 65%), infections (47% vs 59%), and worst Grade 3 or higher infections (10% vs 24%). Across all other categories, the incidence of worst Grade 3 or higher events was similar.

3. AEs by R/R Subgroup

Among subjects with FL, compared with subjects who had relapsed, subjects with refractory disease showed a trend toward a higher incidence of axicabtagene ciloleucel-related SAEs (23% vs 35%) and serious CRS (5% vs 15%). Across all other categories, the incidence of worst Grade 3 or higher events was similar.

4. AEs by Double Refractory Subgroup

Among subjects with FL, compared with subjects who were not in the double refractory subgroup, subjects in the double refractory subgroup showed a trend towards a higher incidence of SAEs (42% vs 56%), axicabtagene ciloleucel-related SAEs (24% vs 47%), worst Grade 3 or higher axicabtagene ciloleucel-related SAEs (18% vs 28%), and serious neurologic events (11% vs 25%).

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been conducted.

Discontinuation due to adverse events

N/A.

Post marketing experience

Axicabtagene ciloleucel was first approved in the US on 18 October 2017 and is currently approved under the trade name YESCARTA® in 36 countries including the US, Canada, Switzerland, Australia, Israel, and the European Economic Area (31 countries).

Postmarketing data are provided in a periodic safety update report/ periodic benefit-risk evaluation report (PBRER) for axicabtagene ciloleucel that covers the 6-month period from 18 April 2020 to 17 October 2020 and summarized here.

As of 17 October 2020, 789 subjects have been exposed to axicabtagene ciloleucel in company sponsored interventional clinical trials. During the reporting period (18 April 2020 to 17 October 2020) approximately 43 subjects were administered axicabtagene ciloleucel in company sponsored clinical trials. In the postmarketing setting, cumulative exposure to axicabtagene ciloleucel was approximately 3666 patients as of 17 October 2020. During the reporting period, approximately 858 patients were administered axicabtagene ciloleucel in the postmarketing setting.

During the reporting period 18 April 2020 to 17 October 2020, the axicabtagene ciloleucel company core data sheet was updated twice. The first update, on 13 May 2020, included opportunistic infection data that further characterizes the known axicabtagene ciloleucel risk Infections. In addition, the CRS and neurologic toxicity grading and management guidances were revised and the 9-month interim data from ZUMA-5 were added. The second update, on 24 July 2020, included the 12-month primary analysis data from ZUMA-5. These updates will be incorporated into product information globally.

No significant safety issues for axicabtagene ciloleucel emerged following the commercialization of this product, and the overall benefit-risk evaluation for axicabtagene ciloleucel continues to be positive.

2.6.1. Discussion on clinical safety

The safety database included 124 FL patients treated with axicabtagene ciloleucel in the ZUMA-5 trial. The initial analysis cutoff date is March 12, 2020, which represents the 12 months follow-up data. Additional safety data were provided from the follow-up analysis 1, with a data cutoff date of 14 September 2020. This prespecified analysis was performed when at least 80 subjects with FL had had the opportunity to be followed for 18 months after axicabtagene ciloleucel infusion (the median actual study follow-up time was 20.34 months, range: 0.3 to 37.7 months; 73% had a potential study follow-up time of at least 18 months). For this assessment report, mostly the data from the 18 months follow-up were used. Yet the 18 months follow up is still considered rather short.

Essentially, the AEs and risks are similar to what has been described for other CAR T cell therapies and for axicabtagene ciloleucel in the other indications. No further risks and AEs could be identified which would be specific for axicabtagene ciloleucel or for the indication to be treated with KTE-X19. The toxicity management plans are presented in the SmPC and are in line with the general management plans for this product class.

The important identified risks (CRS, neurologic events, cytopenias, infections, and hypogammaglobulinemia) were largely reversible and manageable with supportive care and medical interventions.

In general, a lower incidence of CRS (78%) and worst Grade 3 CRS (6%) was observed in the FL patients in the ZUMA-5 study (vs. 93% and 9%, respectively, in patients with aggressive lymphoma; ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, ZUMA-9 Cohort 1, and ZUMA-12). This aspect could be attributed to the indolent type of the disease, but also the increased awareness in the clinical sites and the experience in treating CRS patients.

In addition, the number of patients with neurologic AEs (56%) and worst Grade 3 or higher neurologic AEs (15%) in the FL patients in the ZUMA-5 study seems to be a bit lower than what is known for this drug class (vs. 68% and 31%, respectively, in patients with aggressive lymphoma; ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, ZUMA-9 Cohort 1, and ZUMA-12). However, six subjects with FL had Grade 1 or 2 neurologic events with an onset > 80 days after the axicabtagene ciloleucel infusion, 2 of which were deemed related to axicabtagene ciloleucel. There were 11 subjects with FL who had neurologic events that occurred > 30 days but < 200 days after the axicabtgene ciloleucel infusion. All of these neurologic events

were Grade 1 except for the events of Grade 2 amnesia and Grade 2 confusional state in 1 FL subject. Three subjects with FL had neurologic events that were present beyond study Day 200, two of which were deemed related to axicabtagene ciloleucel. Therefore, there might be a tendency for late neurotoxicity in this setting. The MAH was requested to provide further analysis on the potential causes of such late toxicities, and to provide an in-depth analysis of late neurotoxicity incidence across all patients treated with axicabtagene ciloleucel and brexucabtagene autoleucel. The analysis provided did not identify a consistent pattern in either the time to onset or common etiology for these neurologic events. It is considered though unlikely, that the toxicity from previous lines of chemotherapy would cause these late neurotoxicites, as alluded to by the MAH. Nonetheless, the MAH should further explore this in the future. It is agreed that the SmPC does not need to be modified at this stage, as the late neurotoxicities were reported as low grade toxicities.

Among the important potential risks, no secondary malignancies were attributed to axicabtagene ciloleucel, no confirmed cases of immunogenicity were identified, no subjects tested positive for RCR, no cases of TLS or GvHD were identified.

There was a slight tendency toward a higher incidence of hypogammaglobulinemia (14% vs 27%), worst Grade 3 or higher axicabtagene ciloleucel-related AEs (52% vs 65%), infections (47% vs 59%), and worst Grade 3 or higher infections (10% vs 24%) in females. This trend was already observed for axicabtagene ciloleucel in the previous indication; however, no potential causes were identified so far, and seems to occur irrespective of the indication.

Compared with subjects who had relapsed, subjects with refractory disease showed a trend toward a higher incidence of axicabtagene ciloleucel-related SAEs (23% vs 35%) and serious CRS (5% vs 15%). Additionally, compared with subjects who were not in the double refractory subgroup, subjects in the double refractory subgroup showed a trend towards a higher incidence of SAEs (42% vs 56%), axicabtagene ciloleucel-related SAEs (24% vs 47%), worst Grade 3 or higher axicabtagene ciloleucel-related SAEs (18% vs 28%), and serious neurologic events (11% vs 25%). These aspects seem to be specific for these disease subgroups and dependent of disease status.

2.6.2. Conclusions on clinical safety

The important identified risks for axicabtagene ciloleucel in the FL indication are CRS, neurotoxicity, cytopenias, infections, hypogammaglobulinemia. There are some potential risks linked to the use of this product: secondary malignancy, immunogenicity, RCR, tumor lysis syndrome, and aggravation of GvHD.

Essentially, the AEs and risks are similar to what has been described for other CAR T cell therapies and for axicabtagene ciloleucel in the previous indication. No further risks and AEs could be identified which would be specific for axicabtagene ciloleucel or for the indication to be treated with axicabtagene ciloleucel.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 7.0 with this application. The (main) proposed RMP changes are summarized in the below sections.

General comments:

RMP Part I "Product overview" section "indication(s) in the EEA" has been amended to include the new indication of axicabtagene ciloleucel. Since the current indications (DLBCL and PMBCL) have been added as proposed indications, amendments to this section are warranted. Only the new applied indication should be mentioned as "proposed".

Safety Specification

Epidemiology of the indications and target population

Module SI 'Epidemiology of the indication and target population' was updated satisfactorily to include epidemiology data for the proposed new indication of adult patients with relapsed or refractory follicular lymphoma after three or more lines of systemic therapy.

Clinical trial exposure

Module SIII 'Clinical trial exposure' was adequately updated with regard to exposure information about e.g. dosage, duration, age group, gender, dose, ethnic origin for the proposed FL indication of axicabtagene ciloleucel.

Populations not studied in clinical trials

Module SIV 'Populations not studied in clinical trials' – SIV.1 was updated with the ZUMA-5 study exclusion criteria. Additionally, section SIV.2 and SIV.3 were updated to include data from the ZUMA-5 study. The proposed changes are considered acceptable.

Post-authorisation experience

Module SV 'Post-authorisation experience' was adequately updated with a new estimate of the postmarketing exposure.

Identified and potential risks

In the Module SVII, section SVII.3.1 'Details of important identified risks, important potential risks, and missing information" has been updated with data from the ZUMA-5 study. The proposed changes are considered acceptable.

Missing information

In the Module SVII, the subsection 'Use in non-Caucasian patient populations' under section SVII.3.2 'missing information' was updated to include data from the ZUMA-5 study. The proposed changes are considered acceptable.

Summary of the safety concerns

No changes were proposed by the MAH to the summary of safety concerns. This is considered acceptable as initially no new safety concerns were identified from the submitted data.

Important Identified Risks	Serious neurologic adverse reactions including cerebral oedema
	CRS
	Cytopenias including aplastic anaemia
	Infections
	Hypogammaglobulinaemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	RCR
	TLS
	Aggravation of GvHD
	Transmission of infectious agents via product
	Decrease in viability of the product due to inappropriate preparation of infusion
	CD19 negative relapse
	CAR-T persistence in relapsed patients
	Failure to produce a viable CAR-T cell product
Missing Information	Use in pregnancy and lactation
	Use in non-Caucasian patient populations
	New occurrence or exacerbation of an autoimmune disorder
	Long term safety

Pharmacovigilance plan

Routine pharmacovigilance activities

Specific Adverse Reaction/Adverse Event Follow-up Questionnaires

Name of Questionnaire	Description
Neurologic events	Targeted follow-up questionnaires for neurologic AEs (including serious neurologic adverse reactions) will be utilized as follow up to AE reports to determine start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history, additional medications.

Name of Questionnaire	Description
CRS	Targeted follow-up questionnaires for CRS will be utilized as follow up to an ADR report to determine start and stop dates of the event, severity and seriousness, outcome, diagnostic results, whether alternative causes for signs and symptoms were ruled out, treatment provided, relevant medical history, additional medications. This questionnaire will also collect information on patients with underlying organ impairments (e.g., hepatic, renal, cardiac, pulmonary) who experience CRS.
New malignancy	Targeted follow-up questionnaires for new malignancy will be utilized as follow up to AE reports to obtain further information regarding start and stop dates of the event, severity and seriousness, diagnostic results, pre-existing factors that may have contributed to the development of the new malignancy, relevant medical history and additional medications.
CD19 and CAR T Levels after Recurrence Following Initial Response to Yescarta	Targeted follow-up questionnaires for "CD19 and CAR T levels after recurrence following initial response to Yescarta" will be utilized as a follow-up to AE reports to obtain further information regarding date of diagnosis, diagnostic results (CD19 status in tissue biopsy, presence of CAR T post infusion and at recurrence in blood), and additional information in case of CD19 negativity.

The RMP was updated to include new targeted follow-up questionnaire of CD19 and CAR-T Levels after Recurrence Following Initial Response to Yescarta for the important potential risks of CD19 Negative Relapse and CAR-T Persistence in Relapsed Patients. The proposed targeted follow-up questionnaire is endorsed.

Additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
KT-EU-471-0117 (PASS): Long-term, non-interventional study of recipients of Yescarta for treatment of relapsed or refractory DLBCL and PMBCL Ongoing	Additional characterization of the identified risks, further evaluation of potential risks and missing information.	Identified risks, potential risks, and missing information	Final Report Submission	14 Nov 2040
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
KT-EU-471-0116 (Prescriber survey): Quantitative testing of HCP knowledge about YESCARTA (axicabtagene ciloleucel) risk minimization measures Ongoing	To assess the prescribers' understanding of the risks of Yescarta	Serious neurologic adverse reactions including cerebral edema CRS Infections Secondary malignancies Decrease in viability of the product due to inappropriate preparation of infusion	Final study report	Submitted on 24 June 2021

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
KTE-C19-101 (ZUMA-1) A Phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive NHL Ongoing	To assess safety and efficacy of axicabtagene ciloleucel in refractory aggressive NHL	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD CD19 negative relapse CAR T persistence in relapsed patients Failure to produce a viable CAR T cell product Use in non-Caucasian patient populations New occurrence of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final report Cohort 1 and 2	31 Aug 2031
			Final report Cohort 3	31 Oct 2032
KTE-C19-105 (ZUMA-5): A Phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory iNHL Ongoing	To assess efficacy and safety of axicabtagene ciloleucel in subjects with relapsed/refractory iNHL	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD CD19 negative relapse CAR T persistence in relapsed patients Failure to produce a viable CAR T cell product Use in non-Caucasian patient populations New occurrence of an autoimmune disorder Long term safety	Safety updates in the nearest PSUR to the annual anniversary	Annual
			Final report	30 Apr 2036
KTE-C19-106 (ZUMA-6): A Phase 1-2 multi-center study evaluating the safety and efficacy of KTE C19 in	To assess efficacy and safety of axicabtagene ciloleucel in combination with	Serious neurologic adverse reactions including cerebral edema CRS Cytopenias including aplastic anemia Infections	Safety updates in the nearest PSUR to the annual anniversary	Annual

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
combination with Atezolizumab in subjects with refractory DLBCL Ongoing	atezolizumab in refractory DLBCL subjects	Hypogammaglobulinemia Secondary malignancy Immunogenicity RCR TLS Aggravation of GvHD CD19 negative relapse CAR T persistence in relapsed patients Failure to produce a viable CAR T cell product Use in non-Caucasian patient populations New occurrence of an autoimmune disorder Long term safety	Final report	31 Aug 2033

Overall conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The study(ies) in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorization efficacy studies.

Risk minimisation measures

Routine risk minimisation measures

Safety concern	Routine risk minimization activities
Serious neurologic adverse reactions including cerebral edema	**Routine risk communication**: SmPC sections: 4.2, 4.4, 4.7 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of serious neurologic adverse reactions, including treatment algorithms, are included in the SmPC sections 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information**:

Safety concern	Routine risk minimization activities
	Use restricted to physicians experienced in the treatment of hematological cancers.
CRS	**Routine risk communication**: SmPC sections: 4.2, 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring and management of CRS, including treatment algorithms, are included in the SmPC sections 4.2 and 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Cytopenias including aplastic anemia	**Routine risk communication**: SmPC sections: 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for blood count monitoring is included in SmPC sections 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Infections	**Routine risk communication**: SmPC sections: 4.2, 4.4 and 4.8 PL section: 2, 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for monitoring the signs and symptoms of infection before, during and after Yescarta infusion and treatment are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Hypogammaglobulinemia	**Routine risk communication**: SmPC sections: 4.4 and 4.8 PL section: 4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations for monitoring immunoglobulin levels and management using infection precautions, antibiotic prophylaxis and immunoglobulin replacement are included in SmPC section 4.4.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers.
Secondary malignancy	**Routine risk communication**: SmPC sections: 4.4 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendation for life-long monitoring for secondary malignancies is included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Immunogenicity	**Routine risk communication**: SmPC sections: 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
RCR	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers

Safety concern	Routine risk minimization activities
TLS	**Routine risk communication**: SmPC section: 4.4 PIL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Recommendations that patients with elevated uric acid or high tumor burden receive treatment prior to infusion, and for monitoring and management of TLS are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Aggravation of GvHD	**Routine risk communication**: SmPC section 4.4 PL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Transmission of infectious agents via product	**Routine risk communication**: SmPC Sections 4.2 PL Section 3 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
Decrease in viability of the product due to inappropriate preparation of infusion	**Routine risk communication**: SmPC section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
CD19 negative relapse	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**:

Safety concern	Routine risk minimization activities
	None **Other routine risk minimization measures beyond the Product Information**: None
CAR T persistence in relapsed patients	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
Failure to produce a viable CAR T cell product	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
Use in pregnancy and lactation	**Routine risk communication**: SmPC sections: 4.6 PL section: 2 **Routine risk minimization activities recommending specific clinical measures to address the risk**: Requirement for verification of pregnancy status of women of child-bearing potential included in SmPC section 4.6. Recommendation to refer to information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy in SmPC section 4.6 and PL section 2. **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Use in non-Caucasian patient populations	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: None
New occurrence or exacerbation of an autoimmune disorder	**Routine risk communication**: SmPC section 5.1

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.
Long term safety	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other routine risk minimization measures beyond the Product Information**: Use restricted to physicians experienced in the treatment of hematological cancers.

Only minor editorial amendments have been executed for the routine risk minimization measures. The proposed changes to RMP Part V are considered acceptable.

Additional risk minimisation measures

Additional Risk Minimization Activity: HCP Educational Material

HCP Educational Material	
Objective(s)	To inform HCPs on how to monitor and manage symptoms associated with CRS and serious neurologic adverse reactions and provide guidance on reporting these serious adverse reactions associated with Yescarta.
Rationale for the additional risk minimization activity	The HCP educational material will be provided at launch of the product and at the time of updates in each member state and will highlight the risks of Yescarta and will help ensure that the HCPs using Yescarta are made aware of the risks and will be able to monitor for them. The HCP educational material will also help HCPs ensure that they have access to a minimum of 1 dose of tocilizumab prior to Yescarta infusion. The treatment center must have access to an additional dose of tocilizumab within 8 hours of each previous dose. CRS is not commonly observed with most anti-cancer medications. Therefore, HCPs may not be as experienced in managing these adverse reactions. CRS occurred in 93% of patients in ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, and 82% of patients in ZUMA-5. The median time to onset for CRS was 2 days for patients in ZUMA-1 and 4 days for patients in ZUMA-5, whilst the median time to onset for neurologic events was 5 days for patients in ZUMA-1 Phase 1 and Phase 2 Cohorts 1 and 2, and 7 days for patients in ZUMA-5. It is anticipated that HCP educational material will enhance early diagnosis and proper evidence-based management of these events, including information on when and how to use tocilizumab and/or steroids. The expected result is improvement in the outcomes of or mitigating severe, life-threatening, and fatal CRS and/or neurologic adverse reactions.
Target audience and planned distribution path	The HCP educational material targets HCPs who are likely to prescribe Yescarta. The method of delivery of the HCP educational material is determined on a Member State basis to align with local clinical organization.

HCP Educational Material	
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of HCP educational material will include the following: ▪ Evaluations of HCPs' understanding of the risks of Yescarta by means of a prescriber survey. The objective of the prescriber survey is to assess the prescribers' understanding of the risks of Yescarta. ▪ To meet this objective, the prescriber survey will: o Assess whether every prescriber received the HCP educational material. o Measure the prescribers' understanding of known important identified risks associated with Yescarta. o Assess whether prescribers understand how to identify and treat CRS or serious neurologic adverse reactions. ▪ A post-marketing registry will assess the incidence of serious neurologic adverse reactions and CRS and will thus provide an outcome measure of the effectiveness of the risk minimization program. ▪ A summary of all reported severe, life-threatening CRS and serious neurologic adverse reactions with an analysis of AEs outcomes and treatment. This will be presented within periodic safety reports. These activities will assess whether the HCP educational material is meeting its objectives. If the conclusion is that it is not, Kite Pharma will discuss with the Agency ways that this additional risk minimization activity can be modified.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; HCP = healthcare professional.

Additional Risk Minimization Activity: PAC

PAC

Objective(s)	To inform patients of the risks of CRS and serious neurologic adverse reactions, associated with Yescarta. For patients to share the information in the PAC with their HCPs.
Rationale for the additional risk minimization activity	Easy and immediate patients' access to information about the common signs and symptoms of CRS, and serious neurologic adverse reactions will promote early medical attention and treatment that will help mitigating the risks.
Target audience and planned distribution path	The target audience is patients who will be treated with Yescarta. The PAC will be part of the health care professional kit and will be provided to the patient by the hematologist/heme oncologist or nursing staff.
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of the PAC will include the following: ▪ Prescriber survey to assess the physicians' understanding of the key risks associated with Yescarta (e.g., CRS, serious neurologic adverse reactions). ▪ Collection of evidence that the PAC has been provided to patients treated with Yescarta. These activities will assess the effectiveness of the PAC in meeting its objective. If the conclusion is that the objective is not being met, Kite Pharma will discuss with the Agency ways that this additional risk minimization activity can be modified.

Abbreviations: CRS = cytokine release syndrome; HCP = healthcare professional; PAC = patient alert card.

Additional Risk Minimization Activity: Controlled Distribution Program

Controlled Distribution Program	
Objective(s)	To ensure that Yescarta is only administered in a qualified clinical setting.
Rationale for the additional risk minimization activity	To minimize the important risks of CRS and neurologic adverse reactions, clinical facilities are required to complete a formal site qualification process prior to ordering Yescarta.
Target audience and planned distribution path	The controlled distribution program targets clinical facilities in which Yescarta is administered. The process of qualification is carried out by the QA Site Qualification EU team at Kite Pharma EU BV. The site qualification process includes the following steps: ▪ Introduction to key Yescarta processes ▪ Quality Audit ▪ Training of HCPs ▪ "Dry-run exercise" ▪ Continued monitoring of compliance
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of the controlled distribution program will include the following: ▪ Collection of evidence for the training delivered to HCPs and other relevant site personnel during site qualification. ▪ A post-marketing registry will assess the incidence of serious neurologic adverse reactions and CRS and will thus provide an outcome measure of the effectiveness of the risk minimization program. ▪ A summary of all reported severe, life-threatening CRS and serious neurologic adverse reactions with an analysis of AE outcomes and treatment. This will be presented within periodic safety reports. These activities will assess whether the Controlled Distribution Program is meeting its objectives. Effectiveness of the controlled distribution program will be reported in the PSUR. If the conclusion is that it is not, Kite Pharma will discuss with the Agency ways that this additional risk minimization activity can be modified.

Abbreviations: AE = adverse event; CRS = cytokine release syndrome; HCP = healthcare professional; PSUR = periodic safety update report; QA = quality assurance.

Additional Risk Minimization Activity: Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies

Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies	
Objective(s)	To ensure the appropriate handling, preparation and administration of Yescarta, and raise awareness of the SmPC recommendations for additional testing in case of secondary malignancy.
Rationale for the additional risk minimization activity	To minimize the potential risks of decrease in viability of the product due to inappropriate preparation of the Yescarta infusion and secondary malignancy, HCPs will receive training materials which include instructions on the appropriate handling, preparation and administration of Yescarta and on sampling and management recommendations for secondary malignancies.
Target audience and planned distribution path	The Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies will target HCPs who are likely to be involved in the preparation of the Yescarta infusion and to the prescriber. The exact method of delivery of the HCP educational material will be determined on a Member State basis to align with local clinical organization.
Plans to evaluate the effectiveness of the interventions and criteria for success	The evaluation of the effectiveness of the Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies includes the following: ▪ Collection of evidence that the training was delivered to HCPs and other relevant site personnel during site qualification. ▪ Prescriber survey will assess understanding of the key risk minimization messages associated with handling and administration of Yescarta. These activities will assess the effectiveness of the Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies in meeting its objective. If the conclusion is that the objective is not being met, Kite Pharma will discuss with the Agency ways that this additional risk minimization activity can be modified.

The section "Additional Risk Minimization Activity: Healthcare Provider (HCP) educational Material - Rationale for the additional risk minimization activity" has been updated to include median time to onset and frequency for events of cytokine release syndrome (CRS) from both ZUMA-1 and ZUMA-5.

Section V.3 "Summary of risk minimization measures" has been updated with minor editorial amendments. Additionally, updates to this section were made in accordance with the updates to Part III (PV Plan) to include event follow-up questionnaire as routine pharmacovigilance activity beyond adverse reactions reporting and signal detection for the important potential risks of CD19 negative relapse and CAR-T persistence in relapsed patients, and to align information on additional PhV activities with RMP Part III.2 and III.3.

Summary of risk minimisation measures

Safety Concern	**Risk Minimization Measures**	**Pharmacovigilance Activities**
Important identified risk(s)		
Serious neurologic adverse reactions including cerebral edema	**Routine risk minimization measures**: SmPC sections 4.2, 4.4, 4.7 and 4.8 PL sections 2, 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event follow-up questionnaire

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 KT-EU-471-0116: Submitted on 24 June 2021 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
CRS	**Routine risk minimization measures**: SmPC sections 4.2, 4.4 and 4.8 PL sections 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: ▪ HCP educational material ▪ PAC ▪ Controlled distribution program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event follow-up questionnaire **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 KT-EU-471-0116: Submitted on 24 June 2021 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Cytopenias including aplastic anemia	**Routine risk minimization measures**: SmPC sections 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Infections	**Routine risk minimization measures**: SmPC sections 4.2, 4.4 and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 KT-EU-471-0116: Submitted on 24 Jun 2021 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hypogammaglobulinemia	**Routine risk minimization measures**: SmPC sections 4.4 and 4.8 PL section: 4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Important potential risk(s)		
Secondary malignancy	**Routine risk minimization measures**: SmPC sections 4.4 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event follow-up questionnaire **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 KT-EU-471-0116: Submitted on 24 Jun 2021 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Immunogenicity	**Routine risk minimization measures**: SmPC sections 4.8 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
RCR	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
TLS	**Routine risk minimization measures**: SmPC sections 4.4 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Aggravation of GvHD	**Routine risk minimization measures**: SmPC section 4.4 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Transmission of infectious agents via product	**Routine risk minimization measures**: SmPC Sections 4.2 PL Section 3 **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None
Decrease in viability of the product due to inappropriate preparation of infusion	**Routine risk minimization measures**: SmPC Sections 4.2 **Additional risk minimization measures**: Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0116: Submitted on 24 June 2021
CD19 negative relapse	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event follow-up questionnaire **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
CAR T Persistence in relapsed patients	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Event follow-up questionnaire **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Failure to produce a viable CAR T cell product	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Missing information		
Use in pregnancy and lactation	**Routine risk minimization measures**: SmPC sections 4.6 PL section 2 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040
Use in non-Caucasian patient populations	**Routine risk minimization measures**: None **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
New occurrence or exacerbation of an autoimmune disorder	**Routine risk minimization measures**: SmPC section 5.1 Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033
Long term safety	**Routine risk minimization measures**: Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033

All changes are considered acceptable.

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Elements for a public summary of the RMP

The Part VI: summary of the risk management plan has been updated to include the new indication. The updates made in RMP Parts I through IV have been reflected satisfactorily in the RMP summary.

Annexes

The annexes have been updated as follows:

Part VII Annexes:

- Annex 4: Added new targeted follow-up questionnaires of CD19 and CAR- T Levels after Recurrence Following Initial Response to Yescarta for the important potential risks of CD19 Negative Relapse and CAR-T Persistence in Relapsed Patients. Annex 4 is considered acceptable as it is.

- Annex 6: Updated HCP Educational Material to include follicular lymphoma (FL) and the incidence of CRS and neurologic adverse reactions from ZUMA-5. Annex 6 is considered acceptable as it is.

The following further changes are requested in the next warranted RMP update:

- Annex 8: The MAH updated annex 8 with the changes in this RMP.

Overall conclusion on the RMP

The changes to the RMP in version 7.0 are acceptable.

2.8. Update of the Product Information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Yescarta The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication is: "Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy".

FL is one of the second most common type of lymphomas representing about 10-20% of all NHL. The clinical course of the disease is characterised by relapses, with progressively diminishing remission periods. The majority of patients are diagnosed in advanced stage (III-IV according to Ann Arbor staging). One of the characteristics of the FL immunophenotype is the expression on the surface of tumour cells of CD19, which is a common target for different therapeutic modalities in patients with B-cell malignancies.

3.1.2. Available therapies and unmet medical need

Although newly diagnosed FL of low grade is an indolent disease and patients respond well to first-line chemoimmunotherapy, most of patients relapse and received several treatments with different mechanisms of action in second and third line, including chemoimmunotherapy, immunomodulating agents and PI3K inhibitors. For a small proportion of selected patients stem cell transplant (auto- or allo-SCT) is an option. After 3, 4, 5 and 6 lines of therapy the overall survival is respectively 1.1, 0.9, 0.6 and 0.5 years (Batlevi et al., 2020). The disease remains incurable and there is a risk of histologic transformation to high grade NHL. An unmet need for therapeutic options with novel mechanisms of action and manageable toxicity, especially in late lines of relapsed and/or refractory disease, is recognised in this late clinical setting.

3.1.3. Main clinical studies

The main clinical study supporting this application is the single arm trial ZUMA-5 (KTE-C19-105), a Phase 2 Multicenter Study of Axicabtagene Ciloleucel in Subjects with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma (iNHL), which is ongoing in the US. The study includes patients with two histological types of indolent NHL (iNHL): FL and marginal zone lymphoma (MZL). With regard to the indication R/R FL, only subjects classified FL Grade 1-3a have been included, since FL Grade 3b is treated as de novo DLBCL. The results of the primary (cut-off date 12March 2020) and follow-up 18-month (cut-off date 14Sept 2020), and upon request, follow-up 24-month (cut-off date 31Mar2021) analyses have been submitted.

3.2. Favourable effects

Objective response rate (ORR), defined as complete response (CR) plus partial response (PR) per Lugano classification and central assessment, was 91% (95% CI; 82%, 96%) in FL subjects after 3 or more prior lines of therapy (FAS, leukapheresed patients). The CR rate was 79% in this population corresponding to the intended indication. Median DOR is 38.6 months (95% CI: 24.7, NE)

3.3. Uncertainties and limitations about favourable effects

The treatment benefit cannot be comprehensively and comparatively assessed as it was only studied in a single-arm trial.

The major initial uncertainty was related to the discrepancy in the number of patients with histologically confirmed FL by local and retrospective central histopathological diagnosis. Confirmation of FL by central assessment in all subjects, relevant for the intended marketing authorisation, would be ideal situation. However, the Applicant's approach to provide new sets of populations under consideration of a more recent data cut-off date (31 March 2021), as required, and to revise the data sets for FAS, IAS and SAS by excluding subjects with centrally confirmed non-FL (n=5 subjects), is considered acceptable, given that the following revision of the gathered efficacy and safety results in the intended target population did not indicate clinically significant changes. It is known from scientific literature that a reliable pathological diagnosis of FL depends largely on size and quality of the tissue sample, and that discordant histological findings across different biopsies are often observed.

3.4. Unfavourable effects

The AEs reported are similar to what has been described for other CAR T cell therapies and for axicabtagene ciloleucel in the other indications.

The most significant and frequently occurring adverse reactions were CRS (77%), infections (59%) and encephalopathy (47%).

Serious adverse reactions occurred in 45% of patients. The most common serious adverse reactions included encephalopathy (16%), unspecified pathogen infections (12%), CRS (12%), bacterial infections (5%), fever (4%), viral infection (4%) and thrombosis (3%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (14%), unspecified pathogen infections (11%) and CRS (6%).

3.5. Uncertainties and limitations about unfavourable effects

The safety database included 124 FL patients treated with axicabtagene ciloleucel in the ZUMA-5 trial. Yet, the potential follow-up time of 18 months is still rather short. While this period would be enough to identify the earlier and immediate AEs, there are certain potential risks for which conclusive data could not be obtained due to the limited follow-up time. Therefore, aspects regarding secondary malignancies, replication competent retrovirus analysis will be collected in the PASS registry study for the long-term follow-up.

The number of late neurologic toxicities gave additional uncertainties. Similarly, the higher incidence of toxicities in females remains an uncertainty for this product.

3.6. Effects Table

Table 24. Effects Table for Yescarta in follicular lymphoma (FL) excluding centrally confirmed non-FL subjects (data cut-off: 31 March 2021); FAS (n=75) for efficacy and SAS for safety

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR			91% (82, 96)		Single-arm trial, no comparison possible	
CR (after 3 or more prior therapy lines)			77% (66%, 86%)		Single-arm trial	
DOR (KM-median estimate)			38,6 months	N/A	Single-arm trial, no comparison possible	
Unfavourable Effects						
Cytokine Release Syndrome (CRS)	≥ Grade 3	% (n/n)	6% (8/124)	N/A	Strong evidence for relationship to the treatment with axicabtagene ciloleucel	
CART-related encephalopathy syndrome (CRES)	≥ Grade 3	% (n/n)	14% (17/124)	N/A	Strong evidence for relationship to the treatment with axicabtagene ciloleucel.	
Infections	≥ Grade 3	% (n/n)	11%	N/A	Possibly related to conditioning chemotherapy	

Abbreviations: N/A= not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The observed high ORR and CR rates supported by DOR data designate that clinically meaningful benefit could be achieved at long term in the intended population of relapsed or refractory follicular lymphoma (FL) patients in 4L+ setting with poor prognosis and progressively increasing refractoriness to prior therapeutic modalities.

The most important unfavourable effects of axicabtagene ciloleucel as a CAR T cell product in general are CRS, neurotoxicity, cytopenias, infections and hypogammaglobulinaemia. Generally these unfavourable effects are either treatable or have a self-limiting course and are reversible. The potential serious consequences of CRS have been recognised and treatment algorithms have been developed that are still being refined according to further experience. Overall considering the life-threatening disease the safety profile of KTE-X19 seems to be acceptable for the target population. Since the unfavourable effects are in line with the experience made with this drug class, the identified uncertainties and limitations are of limited relevance.

3.7.2. Balance of benefits and risks

While compelling ORR and CR were reported and the depth of responses appears to be accompanied by their durability, uncertainty remains regarding the true magnitude of the effects, especially at long term, i. e. after Month 24. The currently limited follow-up does not allow to fully contextualise response data based on PFS/OS results. The safety database is considered sufficiently characterised due to data available in other patient populations, the toxicity is manageable and no new safety signals have been reported.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of axicabtagene is positive for adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CAT considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy. Consequently, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC and Package Leaflet are proposed to be updated. As a consequence, the RMP (version 7.0) has been updated to align with the indication extension.

In addition, the applicant has taken the opportunity to make minor editorial corrections throughout the SmPC and package leaflet. Lastly, the newly assigned ATC code has been included in the SmPC.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Yescarta is not similar to Gavyzaro and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (See appendix 1).

Additional market protection

Furthermore, the CAT reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Yescarta-H-C-004480/II/0042"